

TITLE OF THE INVENTION

DI-ARYL SUBSTITUTED PYRROLE MODULATORS OF METABOTROPIC GLUTAMATE RECEPTOR-5

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BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention is directed to pyrrole compounds substituted with i) a
10 heteroaryl ring and ii) another heteroaryl or aryl ring with at least one of the rings being further substituted with another ring. In particular, this invention is directed to pyrrole compounds substituted directly, or by a bridge, with i) a heteroaryl moiety containing N adjacent to the point of connection of the heteroaryl and ii) another heteroaryl or aryl ring, with at least one of the rings being further substituted with another ring, which are metabotropic glutamate receptor –
15 subtype 5 (“mGluR5”) modulators useful in the treatment of psychiatric and mood disorders such as, for example, schizophrenia, anxiety, depression, panic, bipolar disorder, and circadian rhythm disorders, as well as in the treatment of pain, Parkinson’s disease, cognitive dysfunction, epilepsy, drug addiction, drug abuse, drug withdrawal, obesity and other diseases.

20 RELATED BACKGROUND

A major excitatory neurotransmitter in the mammalian nervous system is the glutamate molecule, which binds to neurons, thereby activating cell surface receptors. Such surface receptors are characterized as either ionotropic or metabotropic glutamate receptors. The metabotropic glutamate receptors (“mGluR”) are G protein-coupled receptors that activate
25 intracellular second messenger systems when bound to glutamate. Activation of mGluR results in a variety of cellular responses. In particular, mGluR1 and mGluR5 activate phospholipase C, which is followed by mobilizing intracellular calcium.

Modulation of metabotropic glutamate receptor subtype 5 (mGluR5) is useful in the treatment of diseases that affect the nervous system (see for example W.P.J.M Spooren et al.,
30 *Trends Pharmacol. Sci.*, 22:331-337 (2001) and references cited therein). For example, recent evidence demonstrates the involvement of mGluR5 in nociceptive processes and that modulation of mGluR5 using mGluR5-selective compounds is useful in the treatment of various pain states, including acute, persistent and chronic pain [K Walker et al., *Neuropharmacology*, 40:1-9 (2001); F. Bordi, A. Ugolini *Brain Res.*, 871:223-233 (2001)], inflammatory pain [K Walker et

al., *Neuropharmacology*, 40:10-19 (2001); Bhave et al. *Nature Neurosci.* 4:417-423 (2001)] and neuropathic pain [Dogrul et al. *Neurosci. Lett.* 292:115-118 (2000)].

Further evidence supports the use of modulators of mGluR5 in the treatment of psychiatric and neurological disorders. For example, mGluR5-selective compounds such as 2-methyl-6-(phenylethynyl)-pyridine ("MPEP") are effective in animal models of mood disorders, including anxiety and depression [W.P.J.M Spooren et al., *J. Pharmacol. Exp. Ther.*, 295:1267-1275 (2000); E. Tatarczynska et al, *Brit. J. Pharmacol.*, 132:1423-1430 (2001); A. Klodzynska et al, *Pol. J. Pharmacol.*, 132:1423-1430 (2001)]. Gene expression data from humans indicate that modulation of mGluR5 may be useful for the treatment of schizophrenia [T. Ohnuma et al, *Mol. Brain. Res.*, 56:207-217 (1998); *ibid*, *Mol. Brain. Res.*, 85:24-31 (2000)]. Studies have also shown a role for mGluR5, and the potential utility of mGluR5-modulatory compounds, in the treatment of movement disorders such as Parkinson's disease [W.P.J.M Spooren et al., *Europ. J. Pharmacol.* 406:403-410 (2000); H. Awad et al., *J. Neurosci.* 20:7871-7879 (2000); K. Ossawa et al. *Neuropharmacol.* 41:413-420 (2001)]. Other research supports a role for mGluR5 modulation in the treatment of cognitive dysfunction [G. Riedel et al, *Neuropharmacol.* 39:1943-1951 (2000)], epilepsy [A. Chapman et al, *Neuropharmacol.* 39:1567-1574 (2000)] and neuroprotection [V. Bruno et al, *Neuropharmacol.* 39:2223-2230 (2000)]. Studies with mGluR5 knockout mice and MPEP also suggest that modulation of these receptors may be useful in the treatment of drug addiction, drug abuse and drug withdrawal [C. Chiamulera et al. *Nature Neurosci.* 4:873-874 (2001)].

International Patent Publications WO 01/12627 and WO 99/26927 describe heteropolycyclic compounds and their use as metabotropic glutamate receptor antagonists.

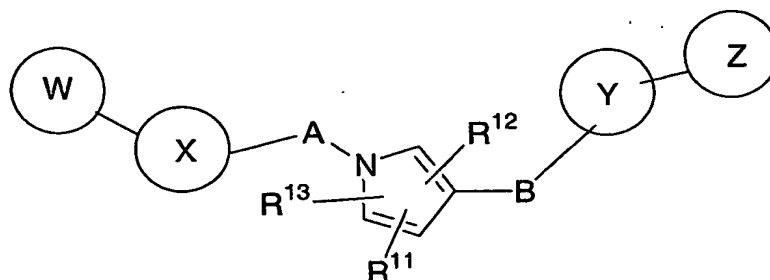
U.S. Patent No. 3,647,809 describes pyridyl-1,2,4-oxadiazole derivatives. U.S. Patent No. 4,022,901 describes 3-pyridyl-5-isothiocyanophenyl oxadiazoles. International Patent Publication WO 98/17652 describes oxadiazoles, WO 97/03967 describes various substituted aromatic compounds, JP 13233767A and WO 94/22846 describe various heterocyclic compounds.

Compounds that include ringed systems are described by various investigators as effective for a variety of therapies and utilities. For example, International Patent Publication No. WO 98/25883 describes ketobenzamides as calpain inhibitors, European Patent Publication No. EP 811610 and U.S. Patent Nos. 5,679,712, 5,693,672 and 5,747,541 describe substituted benzoylguanidine sodium channel blockers, and U.S. Patent No. 5,736,297 describes ring systems useful as a photosensitive composition.

However, there remains a need for novel compounds and compositions that therapeutically inhibit mGluR5 with minimal side effects.

SUMMARY OF THE INVENTION

The present invention is directed to novel pyrroles of Formula (I):



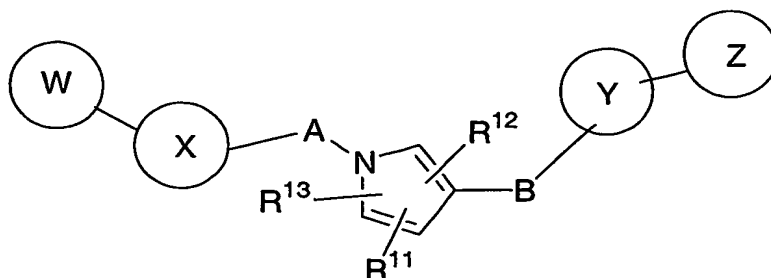
(I)

and pharmaceutically acceptable salts thereof (where A, B, R¹¹, R¹², R¹³, W, X, Y and Z are as defined herein), which are substituted directly, or by a bridge, with i) a heteroaryl moiety containing N adjacent to the point of connection of the heteroaryl and ii) another heteroaryl or aryl ring, with at least one of the rings being further substituted with another ring, which are metabotropic glutamate receptor – subtype 5 modulators useful in the treatment of psychiatric and mood disorders such as, for example, schizophrenia, anxiety, depression, bipolar disorders, and panic, as well as in the treatment of pain, Parkinson's disease, cognitive dysfunction, epilepsy, circadian rhythm and sleep disorders – such as shift-work induced sleep disorder and jet-lag, drug addiction, drug abuse, drug withdrawal, obesity and other diseases. This invention also provides a pharmaceutical composition which includes an effective amount of the novel pyrrole compounds substituted with a heteroaryl moiety, and a pharmaceutically acceptable carrier.

This invention further provides a method of treatment of psychiatric and mood disorders such as, for example, schizophrenia, anxiety, depression, panic, bipolar disorders, and circadian rhythm and sleep disorders, as well as a method of treatment of pain, Parkinson's disease, cognitive dysfunction, epilepsy, obesity, drug addiction, drug abuse and drug withdrawal by the administration of an effective amount of the novel pyrrole compounds substituted with a heteroaryl moiety.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention are represented by Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

X and Y each independently is aryl or heteroaryl wherein at least one of X and Y is a heteroaryl with N adjacent to the position of attachment to A or B respectively;

X is optionally substituted with 1-7 independent halogen, -CN, NO₂, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR¹, -NR¹R², -C(=NR¹)NR²R³, -N(=NR¹)NR²R³, -NR¹COR², -NR¹CO₂R², -NR¹SO₂R⁴, -NR¹CONR²R³, -SR⁴, -SOR⁴, -SO₂R⁴, -SO₂NR¹R², -COR¹, -CO₂R¹, -CONR¹R², -C(=NR¹)R², or -C(=NOR¹)R² substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to X; wherein the -C₁₋₆alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), or -N(C₀₋₆alkyl)(aryl) substituents;

R¹, R², and R³ each independently is -C₀₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

R⁴ is -C₁₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

A is -C₀₋₄alkyl, -C₀₋₂alkyl-SO-C₀₋₂alkyl-, -C₀₋₂alkyl-SO₂-C₀₋₂alkyl-, -C₀₋₂alkyl-CO-C₀₋₂alkyl-, -C₀₋₂alkyl-NR⁹CO-C₀₋₂alkyl-, -C₀₋₂alkyl-NR⁹SO₂-C₀₋₂alkyl- or -heteroC₀₋₄alkyl;

W is -C₃₋₇cycloalkyl, -heteroC₃₋₇cycloalkyl, -C₀₋₆alkylaryl, or -C₀₋₆alkylheteroaryl optionally substituted with 1-7 independent halogen, -CN, NO₂, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR¹, -NR¹R², -C(=NR¹)NR²R³, -N(=NR¹)NR²R³, -

NR¹COR², -NR¹CO₂R², -NR¹SO₂R⁴, -NR¹CONR²R³, -SR⁴, -SOR⁴, -SO₂R⁴, -SO₂NR¹R², -COR¹, -CO₂R¹, -CONR¹R², -C(=NR¹)R², or -C(=NOR¹)R² substituents;

Y is optionally substituted with 1-7 independent halogen, -CN, NO₂, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR⁵, -NR⁵R⁶, -C(=NR⁵)NR⁶R⁷, -N(=NR⁵)NR⁶R⁷, -NR⁵COR⁶,
 5 -NR⁵CO₂R⁶, -NR⁵SO₂R⁸, -NR⁵CONR⁶R⁷, -SR⁸, -SOR⁸, -SO₂R⁸, -SO₂NR⁵R⁶, -COR⁵,
 -CO₂R⁵, -CONR⁵R⁶, -C(=NR⁵)R⁶, or -C(=NOR⁵)R⁶ substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to Y; wherein the -C₁₋₆alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl),
 10 -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), or -N(C₀₋₆alkyl)(aryl) substituents;

R⁵, R⁶, and R⁷ each independently is -C₀₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;
 15

R⁸ is -C₁₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

B is -C₀₋₄alkyl, -C₀₋₂alkyl-SO-C₀₋₂alkyl-, -C₀₋₂alkyl-SO₂-C₀₋₂alkyl-, -C₀₋₂alkyl-CO-C₀₋₂alkyl-, -C₀₋₂alkyl-NR¹⁰CO-C₀₋₂alkyl-, -C₀₋₂alkyl-NR¹⁰SO₂-C₀₋₂alkyl- or -heteroC₀₋₄alkyl;
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R⁹ and R¹⁰ each independently is -C₀₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;
 25

R¹¹, R¹² and R¹³ is each independently halogen, -C₀₋₆alkyl, -C₀₋₆alkoxyl, =O, =N(C₀₋₄alkyl), or -N(C₀₋₄alkyl)(C₀₋₄alkyl), wherein optionally two of R¹¹, R¹² and R¹³ are combined to form a cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring fused to the pyrrole moiety; wherein the -C₁₋₆alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -O(heteroaryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), or -N(C₀₋₆alkyl)(aryl) substituents;
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Z is -C₃₋₇cycloalkyl, -heteroC₃₋₇cycloalkyl, -C₀₋₆alkylaryl, or -C₀₋₆alkylheteroaryl optionally substituted with 1-7 independent halogen, -CN, NO₂, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR¹, -NR¹R², -C(=NR¹)NR²R³, -N(=NR¹)NR²R³, -
 35

NR¹COR², -NR¹CO₂R², -NR¹SO₂R⁴, -NR¹CONR²R³, -SR⁴, -SOR⁴, -SO₂R⁴, -SO₂NR¹R², -COR¹, -CO₂R¹, -CONR¹R², -C(=NR¹)R², or -C(=NOR¹)R² substituents;

one of W and Z is optionally absent; and

any N may be an N-oxide.

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In one aspect, the compounds of this invention are represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein:

X is 2-pyridyl optionally substituted with 1-4 independent halogen, -CN, NO₂, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR¹, -NR¹R², -C(=NR¹)NR²R³, -N(=NR¹)NR²R³,
 10 -NR¹COR², -NR¹CO₂R², -NR¹SO₂R⁴, -NR¹CONR²R³, -SR⁴, -SOR⁴, -SO₂R⁴, -SO₂NR¹R², -COR¹, -CO₂R¹, -CONR¹R², -C(=NR¹)R², or -C(=NOR¹)R² substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to X; wherein the -C₁₋₆alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl),
 15 -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), or -N(C₀₋₆alkyl)(aryl) substituents;

R¹, R², and R³ each independently is -C₀₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;
 20

R⁴ is -C₁₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

A is -C₀₋₄alkyl, -C₀₋₂alkyl-SO-C₀₋₂alkyl-, -C₀₋₂alkyl-SO₂-C₀₋₂alkyl-, -C₀₋₂alkyl-CO-C₀₋₂alkyl-, -C₀₋₂alkyl-NR⁹CO-C₀₋₂alkyl-, -C₀₋₂alkyl-NR⁹SO₂-C₀₋₂alkyl- or -heteroC₀₋₄alkyl;
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W is -C₃₋₇cycloalkyl, -heteroC₃₋₇cycloalkyl, -C₀₋₆alkylaryl, or -C₀₋₆alkylheteroaryl optionally substituted with 1-7 independent halogen, -CN, NO₂, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR¹, -NR¹R², -C(=NR¹)NR²R³, -N(=NR¹)NR²R³, -NR¹COR², -NR¹CO₂R², -NR¹SO₂R⁴, -NR¹CONR²R³, -SR⁴, -SOR⁴, -SO₂R⁴, -SO₂NR¹R², -COR¹, -CO₂R¹, -CONR¹R², -C(=NR¹)R², or -C(=NOR¹)R² substituents;
 30

Y is aryl or heteroaryl optionally substituted with 1-7 independent halogen, -CN, NO₂, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR⁵, -NR⁵R⁶, -C(=NR⁵)NR⁶R⁷, -N(=NR⁵)NR⁶R⁷, -NR⁵COR⁶, -NR⁵CO₂R⁶, -NR⁵SO₂R⁸, -NR⁵CONR⁶R⁷, -SR⁸, -SOR⁸, -SO₂R⁸, -SO₂NR⁵R⁶, -COR⁵, -CO₂R⁵, -CONR⁵R⁶, -C(=NR⁵)R⁶, or -C(=NOR⁵)R⁶
 35

substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to Y; wherein the $-C_{1-6}$ alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, $-CN$, $-C_{1-6}$ alkyl, $-O(C_{0-6}$ alkyl), $-O(C_{3-7}$ cycloalkyl), $-O(aryl)$, $-N(C_{0-6}$ alkyl)(C_{0-6} alkyl), $-N(C_{0-6}$ alkyl)(C_{3-7} cycloalkyl), or $-N(C_{0-6}$ alkyl)(aryl) substituents;

R^5 , R^6 , and R^7 each independently is $-C_{0-6}$ alkyl, $-C_{3-7}$ cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, $-CN$, $-C_{1-6}$ alkyl, $-O(C_{0-6}$ alkyl), $-O(C_{3-7}$ cycloalkyl), $-O(aryl)$, $-N(C_{0-6}$ alkyl)(C_{0-6} alkyl), $-N(C_{0-6}$ alkyl)(C_{3-7} cycloalkyl), $-N(C_{0-6}$ alkyl)(aryl) substituents;

R^8 is $-C_{1-6}$ alkyl, $-C_{3-7}$ cycloalkyl, heteroaryl, or aryl; optionally substituted with 1-5 independent halogen, $-CN$, $-C_{1-6}$ alkyl, $-O(C_{0-6}$ alkyl), $-O(C_{3-7}$ cycloalkyl), $-O(aryl)$, $-N(C_{0-6}$ alkyl)(C_{0-6} alkyl), $-N(C_{0-6}$ alkyl)(C_{3-7} cycloalkyl), $-N(C_{0-6}$ alkyl)(aryl) substituents;

B is $-C_{0-4}$ alkyl, $-C_{0-2}$ alkyl- $SO-C_{0-2}$ alkyl-, $-C_{0-2}$ alkyl- SO_2-C_{0-2} alkyl-, $-C_{0-2}$ alkyl- $CO-C_{0-2}$ alkyl-, $-C_{0-2}$ alkyl- $NR^{10}CO-C_{0-2}$ alkyl-, $-C_{0-2}$ alkyl- $NR^{10}SO_2-C_{0-2}$ alkyl- or $-heteroC_{0-4}$ alkyl;

R^9 and R^{10} each independently is $-C_{0-6}$ alkyl, $-C_{3-7}$ cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, $-CN$, $-C_{1-6}$ alkyl, $-O(C_{0-6}$ alkyl), $-O(C_{3-7}$ cycloalkyl), $-O(aryl)$, $-N(C_{0-6}$ alkyl)(C_{0-6} alkyl), $-N(C_{0-6}$ alkyl)(C_{3-7} cycloalkyl), $-N(C_{0-6}$ alkyl)(aryl) substituents;

R^{11} , R^{12} and R^{13} is each independently halogen, $-C_{0-6}$ alkyl, $-C_{0-6}$ alkoxyl, $=O$, $=N(C_{0-4}$ alkyl), or $-N(C_{0-4}$ alkyl)(C_{0-4} alkyl), wherein optionally two of R^{11} , R^{12} and R^{13} are combined to form a cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring fused to the pyrrole moiety; wherein the $-C_{1-6}$ alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, $-CN$, $-C_{1-6}$ alkyl, $-O(C_{0-6}$ alkyl), $-O(C_{3-7}$ cycloalkyl), $-O(aryl)$, $-O(heteroaryl)$, $-N(C_{0-6}$ alkyl)(C_{0-6} alkyl), $-N(C_{0-6}$ alkyl)(C_{3-7} cycloalkyl), or $-N(C_{0-6}$ alkyl)(aryl) substituents;

Z is $-C_{3-7}$ cycloalkyl, $-heteroC_{3-7}$ cycloalkyl, $-C_{0-6}$ alkylaryl, or $-C_{0-6}$ alkylheteroaryl optionally substituted with 1-7 independent halogen, $-CN$, NO_2 , $-C_{1-6}$ alkyl, $-C_{1-6}$ alkenyl, $-C_{1-6}$ alkynyl, $-OR^1$, $-NR^1R^2$, $-C(=NR^1)NR^2R^3$, $-N(=NR^1)NR^2R^3$, $-NR^1COR^2$, $-NR^1CO_2R^2$, $-NR^1SO_2R^4$, $-NR^1CONR^2R^3$, $-SR^4$, $-SOR^4$, $-SO_2R^4$, $-SO_2NR^1R^2$, $-COR^1$, $-CO_2R^1$, $-CONR^1R^2$, $-C(=NR^1)R^2$, or $-C(=NOR^1)R^2$ substituents;

one of W and Z is optionally absent; and

any N may be an N-oxide.

In an embodiment of this one aspect, the compounds of this invention are represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein:

X is 2-pyridyl optionally substituted with 1-4 independent halogen, -CN, NO₂, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR¹, -NR¹R², -C(=NR¹)NR²R³, -N(=NR¹)NR²R³, -NR¹COR², -NR¹CO₂R², -NR¹SO₂R⁴, -NR¹CONR²R³, -SR⁴, -SOR⁴, -SO₂R⁴, -SO₂NR¹R², -COR¹, -CO₂R¹, -CONR¹R², -C(=NR¹)R², or -C(=NOR¹)R² substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to X; wherein the -C₁₋₆alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), or -N(C₀₋₆alkyl)(aryl) substituents;

R¹, R², and R³ each independently is -C₀₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

R⁴ is -C₁₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

A is -C₀₋₄alkyl, -C₀₋₂alkyl-SO-C₀₋₂alkyl-, -C₀₋₂alkyl-SO₂-C₀₋₂alkyl-, -C₀₋₂alkyl-CO-C₀₋₂alkyl-, -C₀₋₂alkyl-NR⁹CO-C₀₋₂alkyl-, -C₀₋₂alkyl-NR⁹SO₂-C₀₋₂alkyl- or -heteroC₀₋₄alkyl;

W is -C₃₋₇cycloalkyl, -heteroC₃₋₇cycloalkyl, -C₀₋₆alkylaryl, or -C₀₋₆alkylheteroaryl optionally substituted with 1-7 independent halogen, -CN, NO₂, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR⁵, -NR⁵R⁶, -C(=NR⁵)NR⁶R⁷, -N(=NR⁵)NR⁶R⁷, -NR⁵COR⁶, -NR⁵CO₂R⁶, -NR⁵SO₂R⁸, -NR⁵CONR⁶R⁷, -SR⁸, -SOR⁸, -SO₂R⁸, -SO₂NR⁵R⁶, -COR⁵, -CO₂R⁵, -CONR⁵R⁶, -C(=NR⁵)R⁶, or -C(=NOR⁵)R⁶ substituents;

Y is 2-pyridyl optionally substituted with 1-4 independent halogen, -CN, NO₂, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR⁵, -NR⁵R⁶, -C(=NR⁵)NR⁶R⁷, -N(=NR⁵)NR⁶R⁷, -NR⁵COR⁶, -NR⁵CO₂R⁶, -NR⁵SO₂R⁸, -NR⁵CONR⁶R⁷, -SR⁸, -SOR⁸, -SO₂R⁸, -SO₂NR⁵R⁶, -COR⁵, -CO₂R⁵, -CONR⁵R⁶, -C(=NR⁵)R⁶, or -C(=NOR⁵)R⁶ substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to Y; wherein the -C₁₋₆alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), or -N(C₀₋₆alkyl)(aryl) substituents;

R⁵, R⁶, and R⁷ each independently is -C₀-6alkyl, -C₃-7cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, -C₁-6alkyl, -O(C₀-6alkyl), -O(C₃-7cycloalkyl), -O(aryl), -N(C₀-6alkyl)(C₀-6alkyl), -N(C₀-6alkyl)(C₃-7cycloalkyl), -N(C₀-6alkyl)(aryl) substituents;

R⁸ is -C₁-6alkyl, -C₃-7cycloalkyl, heteroaryl, or aryl; optionally substituted with 1-5 independent halogen, -CN, -C₁-6alkyl, -O(C₀-6alkyl), -O(C₃-7cycloalkyl), -O(aryl), -N(C₀-6alkyl)(C₀-6alkyl), -N(C₀-6alkyl)(C₃-7cycloalkyl), -N(C₀-6alkyl)(aryl) substituents;

B is -C₀-4alkyl, -C₀-2alkyl-SO-C₀-2alkyl-, -C₀-2alkyl-SO₂-C₀-2alkyl-, -C₀-2alkyl-CO-C₀-2alkyl-, -C₀-2alkyl-NR¹⁰CO-C₀-2alkyl-, -C₀-2alkyl-NR¹⁰SO₂-C₀-2alkyl- or -heteroC₀-4alkyl;

R⁹ and R¹⁰ each independently is -C₀-6alkyl, -C₃-7cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, -C₁-6alkyl, -O(C₀-6alkyl), -O(C₃-7cycloalkyl), -O(aryl), -N(C₀-6alkyl)(C₀-6alkyl), -N(C₀-6alkyl)(C₃-7cycloalkyl), -N(C₀-6alkyl)(aryl) substituents;

R¹¹, R¹² and R¹³ is each independently halogen, -C₀-6alkyl, -C₀-6alkoxyl, =O, =N(C₀-4alkyl), or -N(C₀-4alkyl)(C₀-4alkyl), wherein optionally two of R¹¹, R¹² and R¹³ are combined to form a cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring fused to the pyrrole moiety; wherein the -C₁-6alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, -CN, -C₁-6alkyl, -O(C₀-6alkyl), -O(C₃-7cycloalkyl), -O(aryl), -O(heteroaryl), -N(C₀-6alkyl)(C₀-6alkyl), -N(C₀-6alkyl)(C₃-7cycloalkyl), or -N(C₀-6alkyl)(aryl) substituents;

Z is -C₃-7cycloalkyl, -heteroC₃-7cycloalkyl, -C₀-6alkylaryl, or -C₀-6alkylheteroaryl optionally substituted with 1-7 independent halogen, -CN, NO₂, -C₁-6alkyl, -C₁-6alkenyl, -C₁-6alkynyl, -OR¹, -NR¹R², -C(=NR¹)NR²R³, -N(=NR¹)NR²R³, -NR¹COR², -NR¹CO₂R², -NR¹SO₂R⁴, -NR¹CONR²R³, -SR⁴, -SOR⁴, -SO₂R⁴, -SO₂NR¹R², -COR¹, -CO₂R¹, -CONR¹R², -C(=NR¹)R², or -C(=NOR¹)R² substituents;

one of W and Z is optionally absent; and

any N may be an N-oxide.

In a second aspect, the compounds of this invention are represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein:

X is aryl or heteroaryl optionally substituted with 1-7 independent halogen, -CN, NO₂, -C₁-6alkyl, -C₁-6alkenyl, -C₁-6alkynyl, -OR¹, -NR¹R², -C(=NR¹)NR²R³, -N(=NR¹)NR²R³, -NR¹COR², -NR¹CO₂R², -NR¹SO₂R⁴, -NR¹CONR²R³, -SR⁴, -SOR⁴, -SO₂R⁴, -SO₂NR¹R², -COR¹, -CO₂R¹, -CONR¹R², -C(=NR¹)R², or -C(=NOR¹)R²

substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to X; wherein the -C₁₋₆alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), or -N(C₀₋₆alkyl)(aryl) substituents;

R¹, R², and R³ each independently is -C₀₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

R⁴ is -C₁₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

A is -C₀₋₄alkyl, -C₀₋₂alkyl-SO-C₀₋₂alkyl-, -C₀₋₂alkyl-SO₂-C₀₋₂alkyl-, -C₀₋₂alkyl-CO-C₀₋₂alkyl-, -C₀₋₂alkyl-NR⁹CO-C₀₋₂alkyl-, -C₀₋₂alkyl-NR⁹SO₂-C₀₋₂alkyl- or -heteroC₀₋₄alkyl;

W is -C₃₋₇cycloalkyl, -heteroC₃₋₇cycloalkyl, -C₀₋₆alkylaryl, or -C₀₋₆alkylheteroaryl optionally substituted with 1-7 independent halogen, -CN, NO₂, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR¹, -NR¹R², -C(=NR¹)NR²R³, -N(=NR¹)NR²R³, -NR¹COR², -NR¹CO₂R², -NR¹SO₂R⁴, -NR¹CONR²R³, -SR⁴, -SOR⁴, -SO₂R⁴, -SO₂NR¹R², -COR¹, -CO₂R¹, -CONR¹R², -C(=NR¹)R², or -C(=NOR¹)R² substituents;

Y is 2-pyridyl optionally substituted with 1-4 independent halogen, -CN, NO₂, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR⁵, -NR⁵R⁶, -C(=NR⁵)NR⁶R⁷, -N(=NR⁵)NR⁶R⁷, -NR⁵COR⁶, -NR⁵CO₂R⁶, -NR⁵SO₂R⁸, -NR⁵CONR⁶R⁷, -SR⁸, -SOR⁸, -SO₂R⁸, -SO₂NR⁵R⁶, -COR⁵, -CO₂R⁵, -CONR⁵R⁶, -C(=NR⁵)R⁶, or -C(=NOR⁵)R⁶ substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to Y; wherein the -C₁₋₆alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), or -N(C₀₋₆alkyl)(aryl) substituents;

R⁵, R⁶, and R⁷ each independently is -C₀₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

R⁸ is -C₁₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

B is -C₀₋₄alkyl, -C₀₋₂alkyl-SO-C₀₋₂alkyl-, -C₀₋₂alkyl-SO₂-C₀₋₂alkyl-, -C₀₋₂alkyl-CO-C₀₋₂alkyl-, -C₀₋₂alkyl-NR¹⁰CO-C₀₋₂alkyl-, -C₀₋₂alkyl-NR¹⁰SO₂-C₀₋₂alkyl- or -heteroC₀₋₄alkyl;

R⁹ and R¹⁰ each independently is -C₀₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

R¹¹, R¹² and R¹³ is each independently halogen, -C₀₋₆alkyl, -C₀₋₆alkoxyl, =O, =N(C₀₋₄alkyl), or -N(C₀₋₄alkyl)(C₀₋₄alkyl), wherein optionally two of R¹¹, R¹² and R¹³ are combined to form a cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring fused to the pyrrole moiety; wherein the -C₁₋₆alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -O(heteroaryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), or -N(C₀₋₆alkyl)(aryl) substituents;

Z is -C₃₋₇cycloalkyl, -heteroC₃₋₇cycloalkyl, -C₀₋₆alkylaryl, or -C₀₋₆alkylheteroaryl optionally substituted with 1-7 independent halogen, -CN, NO₂, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR¹, -NR¹R², -C(=NR¹)NR²R³, -N(=NR¹)NR²R³, -NR¹COR², -NR¹CO₂R², -NR¹SO₂R⁴, -NR¹CONR²R³, -SR⁴, -SOR⁴, -SO₂R⁴, -SO₂NR¹R², -COR¹, -CO₂R¹, -CONR¹R², -C(=NR¹)R², or -C(=NOR¹)R² substituents;

one of W and Z is optionally absent; and
any N may be an N-oxide.

In a third aspect, the compounds of this invention are represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein:

X is phenyl optionally substituted with 1-5 independent halogen, -CN, NO₂, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR¹, -NR¹R², -C(=NR¹)NR²R³, -N(=NR¹)NR²R³, -NR¹COR², -NR¹CO₂R², -NR¹SO₂R⁴, -NR¹CONR²R³, -SR⁴, -SOR⁴, -SO₂R⁴, -SO₂NR¹R², -COR¹, -CO₂R¹, -CONR¹R², -C(=NR¹)R², or -C(=NOR¹)R² substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to X; wherein the -C₁₋₆alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl),

–O(aryl), –N(C₀₋₆alkyl)(C₀₋₆alkyl), –N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), or –N(C₀₋₆alkyl)(aryl) substituents;

R¹, R², and R³ each independently is –C₀₋₆alkyl, –C₃₋₇cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, –CN, –C₁₋₆alkyl, –O(C₀₋₆alkyl), –O(C₃₋₇cycloalkyl), –O(aryl), –N(C₀₋₆alkyl)(C₀₋₆alkyl), –N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), –N(C₀₋₆alkyl)(aryl) substituents;

R⁴ is –C₁₋₆alkyl, –C₃₋₇cycloalkyl, heteroaryl, or aryl; optionally substituted with 1-5 independent halogen, –CN, –C₁₋₆alkyl, –O(C₀₋₆alkyl), –O(C₃₋₇cycloalkyl), –O(aryl), –N(C₀₋₆alkyl)(C₀₋₆alkyl), –N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), –N(C₀₋₆alkyl)(aryl) substituents;

A is –C₀₋₄alkyl, –C₀₋₂alkyl–SO–C₀₋₂alkyl–, –C₀₋₂alkyl–SO₂–C₀₋₂alkyl–, –C₀₋₂alkyl–CO–C₀₋₂alkyl–, –C₀₋₂alkyl–NR⁹CO–C₀₋₂alkyl–, –C₀₋₂alkyl–NR⁹SO₂–C₀₋₂alkyl– or –heteroC₀₋₄alkyl;

W is –C₃₋₇cycloalkyl, –heteroC₃₋₇cycloalkyl, –C₀₋₆alkylaryl, or –C₀₋₆alkylheteroaryl optionally substituted with 1-7 independent halogen, –CN, NO₂, –C₁₋₆alkyl, –C₁₋₆alkenyl, –C₁₋₆alkynyl, –OR¹, –NR¹R², –C(=NR¹)NR²R³, –N(=NR¹)NR²R³, –NR¹COR², –NR¹CO₂R², –NR¹SO₂R⁴, –NR¹CONR²R³, –SR⁴, –SOR⁴, –SO₂R⁴, –SO₂NR¹R², –COR¹, –CO₂R¹, –CONR¹R², –C(=NR¹)R², or –C(=NOR¹)R² substituents;

Y is aryl or heteroaryl optionally substituted with 1-7 independent halogen, –CN, NO₂, –C₁₋₆alkyl, –C₁₋₆alkenyl, –C₁₋₆alkynyl, –OR⁵, –NR⁵R⁶, –C(=NR⁵)NR⁶R⁷, –N(=NR⁵)NR⁶R⁷, –NR⁵COR⁶, –NR⁵CO₂R⁶, –NR⁵SO₂R⁸, –NR⁵CONR⁶R⁷, –SR⁸, –SOR⁸, –SO₂R⁸, –SO₂NR⁵R⁶, –COR⁵, –CO₂R⁵, –CONR⁵R⁶, –C(=NR⁵)R⁶, or –C(=NOR⁵)R⁶ substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to Y; wherein the –C₁₋₆alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, –CN, –C₁₋₆alkyl, –O(C₀₋₆alkyl), –O(C₃₋₇cycloalkyl), –O(aryl), –N(C₀₋₆alkyl)(C₀₋₆alkyl), –N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), or –N(C₀₋₆alkyl)(aryl) substituents;

R⁵, R⁶, and R⁷ each independently is –C₀₋₆alkyl, –C₃₋₇cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, –CN, –C₁₋₆alkyl, –O(C₀₋₆alkyl), –O(C₃₋₇cycloalkyl), –O(aryl), –N(C₀₋₆alkyl)(C₀₋₆alkyl), –N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), –N(C₀₋₆alkyl)(aryl) substituents;

R⁸ is –C₁₋₆alkyl, –C₃₋₇cycloalkyl, heteroaryl, or aryl; optionally substituted with 1-5 independent halogen, –CN, –C₁₋₆alkyl, –O(C₀₋₆alkyl), –O(C₃₋₇cycloalkyl), –O(aryl), –N(C₀₋₆alkyl)(C₀₋₆alkyl), –N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), –N(C₀₋₆alkyl)(aryl) substituents;

B is -C₀₋₄alkyl, -C₀₋₂alkyl-SO-C₀₋₂alkyl-, -C₀₋₂alkyl-SO₂-C₀₋₂alkyl-, -C₀₋₂alkyl-CO-C₀₋₂alkyl-, -C₀₋₂alkyl-NR¹⁰CO-C₀₋₂alkyl-, -C₀₋₂alkyl-NR¹⁰SO₂-C₀₋₂alkyl- or -heteroC₀₋₄alkyl;

R⁹ and R¹⁰ each independently is -C₀₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

R¹¹, R¹² and R¹³ is each independently halogen, -C₀₋₆alkyl, -C₀₋₆alkoxyl, =O, =N(C₀₋₄alkyl), or -N(C₀₋₄alkyl)(C₀₋₄alkyl), wherein optionally two of R¹¹, R¹² and R¹³ are combined to form a cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring fused to the pyrrole moiety; wherein the -C₁₋₆alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -O(heteroaryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), or -N(C₀₋₆alkyl)(aryl) substituents;

Z is -C₃₋₇cycloalkyl, -heteroC₃₋₇cycloalkyl, -C₀₋₆alkylaryl, or -C₀₋₆alkylheteroaryl optionally substituted with 1-7 independent halogen, -CN, NO₂, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR¹, -NR¹R², -C(=NR¹)NR²R³, -N(=NR¹)NR²R³, -NR¹COR², -NR¹CO₂R², -NR¹SO₂R⁴, -NR¹CONR²R³, -SR⁴, -SOR⁴, -SO₂R⁴, -SO₂NR¹R², -COR¹, -CO₂R¹, -CONR¹R², -C(=NR¹)R², or -C(=NOR¹)R² substituents;

one of W and Z is optionally absent; and
any N may be an N-oxide.

In an embodiment of this third aspect, the compounds of this invention are represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein:

X is phenyl optionally substituted with 1-5 independent halogen, -CN, NO₂, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR¹, -NR¹R², -C(=NR¹)NR²R³, -N(=NR¹)NR²R³, -NR¹COR², -NR¹CO₂R², -NR¹SO₂R⁴, -NR¹CONR²R³, -SR⁴, -SOR⁴, -SO₂R⁴, -SO₂NR¹R², -COR¹, -CO₂R¹, -CONR¹R², -C(=NR¹)R², or -C(=NOR¹)R² substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to X; wherein the -C₁₋₆alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), or -N(C₀₋₆alkyl)(aryl) substituents;

R¹, R², and R³ each independently is -C₀₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -

O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

R⁴ is -C₁₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

A is -C₀₋₄alkyl, -C₀₋₂alkyl-SO-C₀₋₂alkyl-, -C₀₋₂alkyl-SO₂-C₀₋₂alkyl-, -C₀₋₂alkyl-CO-C₀₋₂alkyl-, -C₀₋₂alkyl-NR⁹CO-C₀₋₂alkyl-, -C₀₋₂alkyl-NR⁹SO₂-C₀₋₂alkyl- or -heteroC₀₋₄alkyl;

W is -C₃₋₇cycloalkyl, -heteroC₃₋₇cycloalkyl, -C₀₋₆alkylaryl, or -C₀₋₆alkylheteroaryl optionally substituted with 1-7 independent halogen, -CN, NO₂, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR¹, -NR¹R², -C(=NR¹)NR²R³, -N(=NR¹)NR²R³, -NR¹COR², -NR¹CO₂R², -NR¹SO₂R⁴, -NR¹CONR²R³, -SR⁴, -SOR⁴, -SO₂R⁴, -SO₂NR¹R², -COR¹, -CO₂R¹, -CONR¹R², -C(=NR¹)R², or -C(=NOR¹)R² substituents;

Y is 2-pyridyl optionally substituted with 1-4 independent halogen, -CN, NO₂, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR⁵, -NR⁵R⁶, -C(=NR⁵)NR⁶R⁷, -N(=NR⁵)NR⁶R⁷, -NR⁵COR⁶, -NR⁵CO₂R⁶, -NR⁵SO₂R⁸, -NR⁵CONR⁶R⁷, -SR⁸, -SOR⁸, -SO₂R⁸, -SO₂NR⁵R⁶, -COR⁵, -CO₂R⁵, -CONR⁵R⁶, -C(=NR⁵)R⁶, or -C(=NOR⁵)R⁶ substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to Y; wherein the -C₁₋₆alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), or -N(C₀₋₆alkyl)(aryl) substituents;

R⁵, R⁶, and R⁷ each independently is -C₀₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

R⁸ is -C₁₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

B is -C₀₋₄alkyl, -C₀₋₂alkyl-SO-C₀₋₂alkyl-, -C₀₋₂alkyl-SO₂-C₀₋₂alkyl-, -C₀₋₂alkyl-CO-C₀₋₂alkyl-, -C₀₋₂alkyl-NR¹⁰CO-C₀₋₂alkyl-, -C₀₋₂alkyl-NR¹⁰SO₂-C₀₋₂alkyl- or -heteroC₀₋₄alkyl;

R⁹ and R¹⁰ each independently is -C₀₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -

O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

R¹¹, R¹² and R¹³ is each independently halogen, -C₀₋₆alkyl, -C₀₋₆alkoxyl, =O, =N(C₀₋₄alkyl), or -N(C₀₋₄alkyl)(C₀₋₄alkyl), wherein optionally two of R¹¹, R¹² and R¹³ are

combined to form a cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring fused to the pyrrole moiety; wherein the -C₁₋₆alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -O(heteroaryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), or -N(C₀₋₆alkyl)(aryl) substituents;

Z is -C₃₋₇cycloalkyl, -heteroC₃₋₇cycloalkyl, -C₀₋₆alkylaryl, or -C₀₋₆alkylheteroaryl optionally substituted with 1-7 independent halogen, -CN, NO₂, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR¹, -NR¹R², -C(=NR¹)NR²R³, -N(=NR¹)NR²R³, -NR¹COR², -NR¹CO₂R², -NR¹SO₂R⁴, -NR¹CONR²R³, -SR⁴, -SOR⁴, -SO₂R⁴, -SO₂NR¹R², -COR¹, -CO₂R¹, -CONR¹R², -C(=NR¹)R², or -C(=NOR¹)R² substituents;

one of W and Z is optionally absent; and
any N may be an N-oxide.

In a fourth aspect, the compounds of this invention are represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein:

X is aryl or heteroaryl optionally substituted with 1-7 independent halogen, -CN, NO₂, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR¹, -NR¹R², -C(=NR¹)NR²R³, -N(=NR¹)NR²R³, -NR¹COR², -NR¹CO₂R², -NR¹SO₂R⁴, -NR¹CONR²R³, -SR⁴, -SOR⁴, -SO₂R⁴, -SO₂NR¹R², -COR¹, -CO₂R¹, -CONR¹R², -C(=NR¹)R², or -C(=NOR¹)R² substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to X; wherein the -C₁₋₆alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), or -N(C₀₋₆alkyl)(aryl) substituents;

R¹, R², and R³ each independently is -C₀₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

R⁴ is -C₁₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

A is $-C_{0-4}alkyl$, $-C_{0-2}alkyl-SO-C_{0-2}alkyl-$, $-C_{0-2}alkyl-SO_2-C_{0-2}alkyl-$, $-C_{0-2}alkyl-CO-C_{0-2}alkyl-$, $-C_{0-2}alkyl-NR^9CO-C_{0-2}alkyl-$, $-C_{0-2}alkyl-NR^9SO_2-C_{0-2}alkyl-$ or $-heteroC_{0-4}alkyl$;

W is $-C_{3-7}cycloalkyl$, $-heteroC_{3-7}cycloalkyl$, $-C_{0-6}alkylaryl$, or $-C_{0-6}alkylheteroaryl$ optionally substituted with 1-7 independent halogen, $-CN$, NO_2 , $-C_{1-6}alkyl$, $-C_{1-6}alkenyl$, $-C_{1-6}alkynyl$, $-OR^1$, $-NR^1R^2$, $-C(=NR^1)NR^2R^3$, $-N(=NR^1)NR^2R^3$, $-NR^1COR^2$, $-NR^1CO_2R^2$, $-NR^1SO_2R^4$, $-NR^1CONR^2R^3$, $-SR^4$, $-SOR^4$, $-SO_2R^4$, $-SO_2NR^1R^2$, $-COR^1$, $-CO_2R^1$, $-CONR^1R^2$, $-C(=NR^1)R^2$, or $-C(=NOR^1)R^2$ substituents;

Y is 1,3-thiazolyl optionally substituted with 1-2 independent halogen, $-CN$, NO_2 , $-C_{1-6}alkyl$, $-C_{1-6}alkenyl$, $-C_{1-6}alkynyl$, $-OR^5$, $-NR^5R^6$, $-C(=NR^5)NR^6R^7$, $-N(=NR^5)NR^6R^7$, $-NR^5COR^6$, $-NR^5CO_2R^6$, $-NR^5SO_2R^8$, $-NR^5CONR^6R^7$, $-SR^8$, $-SOR^8$, $-SO_2R^8$, $-SO_2NR^5R^6$, $-COR^5$, $-CO_2R^5$, $-CONR^5R^6$, $-C(=NR^5)R^6$, or $-C(=NOR^5)R^6$ substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to Y; wherein the $-C_{1-6}alkyl$ substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, $-CN$, $-C_{1-6}alkyl$, $-O(C_{0-6}alkyl)$, $-O(C_{3-7}cycloalkyl)$, $-O(aryl)$, $-N(C_{0-6}alkyl)(C_{0-6}alkyl)$, $-N(C_{0-6}alkyl)(C_{3-7}cycloalkyl)$, or $-N(C_{0-6}alkyl)(aryl)$ substituents;

R^5 , R^6 , and R^7 each independently is $-C_{0-6}alkyl$, $-C_{3-7}cycloalkyl$, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, $-CN$, $-C_{1-6}alkyl$, $-O(C_{0-6}alkyl)$, $-O(C_{3-7}cycloalkyl)$, $-O(aryl)$, $-N(C_{0-6}alkyl)(C_{0-6}alkyl)$, $-N(C_{0-6}alkyl)(C_{3-7}cycloalkyl)$, $-N(C_{0-6}alkyl)(aryl)$ substituents;

R^8 is $-C_{1-6}alkyl$, $-C_{3-7}cycloalkyl$, heteroaryl, or aryl; optionally substituted with 1-5 independent halogen, $-CN$, $-C_{1-6}alkyl$, $-O(C_{0-6}alkyl)$, $-O(C_{3-7}cycloalkyl)$, $-O(aryl)$, $-N(C_{0-6}alkyl)(C_{0-6}alkyl)$, $-N(C_{0-6}alkyl)(C_{3-7}cycloalkyl)$, $-N(C_{0-6}alkyl)(aryl)$ substituents;

B is $-C_{0-4}alkyl$, $-C_{0-2}alkyl-SO-C_{0-2}alkyl-$, $-C_{0-2}alkyl-SO_2-C_{0-2}alkyl-$, $-C_{0-2}alkyl-CO-C_{0-2}alkyl-$, $-C_{0-2}alkyl-NR^{10}CO-C_{0-2}alkyl-$, $-C_{0-2}alkyl-NR^{10}SO_2-C_{0-2}alkyl-$ or $-heteroC_{0-4}alkyl$;

R^9 and R^{10} each independently is $-C_{0-6}alkyl$, $-C_{3-7}cycloalkyl$, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, $-CN$, $-C_{1-6}alkyl$, $-O(C_{0-6}alkyl)$, $-O(C_{3-7}cycloalkyl)$, $-O(aryl)$, $-N(C_{0-6}alkyl)(C_{0-6}alkyl)$, $-N(C_{0-6}alkyl)(C_{3-7}cycloalkyl)$, $-N(C_{0-6}alkyl)(aryl)$ substituents;

R^{11} , R^{12} and R^{13} is each independently halogen, $-C_{0-6}alkyl$, $-C_{0-6}alkoxyl$, $=O$, $=N(C_{0-4}alkyl)$, or $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, wherein optionally two of R^{11} , R^{12} and R^{13} are combined to form a cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring fused to the pyrrole moiety; wherein the $-C_{1-6}alkyl$ substituent, cycloalkyl ring, or heterocycloalkyl ring each

optionally is further substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -O(heteroaryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), or -N(C₀₋₆alkyl)(aryl) substituents;

Z is -C₃₋₇cycloalkyl, -heteroC₃₋₇cycloalkyl, -C₀₋₆alkylaryl, or -C₀₋₆alkylheteroaryl optionally substituted with 1-7 independent halogen, -CN, NO₂, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR¹, -NR¹R², -C(=NR¹)NR²R³, -N(=NR¹)NR²R³, -NR¹COR², -NR¹CO₂R², -NR¹SO₂R⁴, -NR¹CONR²R³, -SR⁴, -SOR⁴, -SO₂R⁴, -SO₂NR¹R², -COR¹, -CO₂R¹, -CONR¹R², -C(=NR¹)R², or -C(=NOR¹)R² substituents;

one of W and Z is optionally absent; and

any N may be an N-oxide.

In an embodiment of this fourth aspect, the compounds of this invention are represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein:

X is phenyl optionally substituted with 1-5 independent halogen, -CN, NO₂, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR¹, -NR¹R², -C(=NR¹)NR²R³, -N(=NR¹)NR²R³, -NR¹COR², -NR¹CO₂R², -NR¹SO₂R⁴, -NR¹CONR²R³, -SR⁴, -SOR⁴, -SO₂R⁴, -SO₂NR¹R², -COR¹, -CO₂R¹, -CONR¹R², -C(=NR¹)R², or -C(=NOR¹)R² substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to X; wherein the -C₁₋₆alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), or -N(C₀₋₆alkyl)(aryl) substituents;

R¹, R², and R³ each independently is -C₀₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

R⁴ is -C₁₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

A is -C₀₋₄alkyl, -C₀₋₂alkyl-SO-C₀₋₂alkyl-, -C₀₋₂alkyl-SO₂-C₀₋₂alkyl-, -C₀₋₂alkyl-CO-C₀₋₂alkyl-, -C₀₋₂alkyl-NR⁹CO-C₀₋₂alkyl-, -C₀₋₂alkyl-NR⁹SO₂-C₀₋₂alkyl- or -heteroC₀₋₄alkyl;

W is -C₃₋₇cycloalkyl, -heteroC₃₋₇cycloalkyl, -C₀₋₆alkylaryl, or -C₀₋₆alkylheteroaryl optionally substituted with 1-7 independent halogen, -CN, NO₂, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR¹, -NR¹R², -C(=NR¹)NR²R³, -N(=NR¹)NR²R³, -

NR¹COR², -NR¹CO₂R², -NR¹SO₂R⁴, -NR¹CONR²R³, -SR⁴, -SOR⁴, -SO₂R⁴, -SO₂NR¹R², -COR¹, -CO₂R¹, -CONR¹R², -C(=NR¹)R², or -C(=NOR¹)R² substituents;

Y is 1,3-thiazolyl optionally substituted with 1-2 independent halogen, -CN, NO₂, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR⁵, -NR⁵R⁶, -C(=NR⁵)NR⁶R⁷, -N(=NR⁵)NR⁶R⁷, -NR⁵COR⁶, -NR⁵CO₂R⁶, -NR⁵SO₂R⁸, -NR⁵CONR⁶R⁷, -SR⁸, -SOR⁸, -SO₂R⁸, -SO₂NR⁵R⁶, -COR⁵, -CO₂R⁵, -CONR⁵R⁶, -C(=NR⁵)R⁶, or -C(=NOR⁵)R⁶ substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to Y; wherein the -C₁₋₆alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), or -N(C₀₋₆alkyl)(aryl) substituents;

R⁵, R⁶, and R⁷ each independently is -C₀₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

R⁸ is -C₁₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

B is -C₀₋₄alkyl, -C₀₋₂alkyl-SO-C₀₋₂alkyl-, -C₀₋₂alkyl-SO₂-C₀₋₂alkyl-, -C₀₋₂alkyl-CO-C₀₋₂alkyl-, -C₀₋₂alkyl-NR¹⁰CO-C₀₋₂alkyl-, -C₀₋₂alkyl-NR¹⁰SO₂-C₀₋₂alkyl- or -heteroC₀₋₄alkyl;

R⁹ and R¹⁰ each independently is -C₀₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

R¹¹, R¹² and R¹³ is each independently halogen, -C₀₋₆alkyl, -C₀₋₆alkoxyl, =O, =N(C₀₋₄alkyl), or -N(C₀₋₄alkyl)(C₀₋₄alkyl), wherein optionally two of R¹¹, R¹² and R¹³ are combined to form a cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring fused to the pyrrole moiety; wherein the -C₁₋₆alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -O(heteroaryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), or -N(C₀₋₆alkyl)(aryl) substituents;

Z is -C₃₋₇cycloalkyl, -heteroC₃₋₇cycloalkyl, -C₀₋₆alkylaryl, or -C₀₋₆alkylheteroaryl optionally substituted with 1-7 independent halogen, -CN, NO₂, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR¹, -NR¹R², -C(=NR¹)NR²R³, -N(=NR¹)NR²R³, -

NR¹COR², -NR¹CO₂R², -NR¹SO₂R⁴, -NR¹CONR²R³, -SR⁴, -SOR⁴, -SO₂R⁴, -SO₂NR¹R², -COR¹, -CO₂R¹, -CONR¹R², -C(=NR¹)R², or -C(=NOR¹)R² substituents;

one of W and Z is optionally absent; and

any N may be an N-oxide.

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In a fifth aspect, the compounds of this invention are represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein:

X is aryl or heteroaryl optionally substituted with 1-7 independent halogen, -CN, NO₂, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR¹, -NR¹R², -C(=NR¹)NR²R³, -

10 N(=NR¹)NR²R³, -NR¹COR², -NR¹CO₂R², -NR¹SO₂R⁴, -NR¹CONR²R³, -SR⁴, -SOR⁴, -SO₂R⁴, -SO₂NR¹R², -COR¹, -CO₂R¹, -CONR¹R², -C(=NR¹)R², or -C(=NOR¹)R²

substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to X; wherein the -C₁₋₆alkyl substituent, cycloalkyl ring, or

15 heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), or -N(C₀₋₆alkyl)(aryl) substituents;

R¹, R², and R³ each independently is -C₀₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

20 R⁴ is -C₁₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

25 A is -C₀₋₄alkyl, -C₀₋₂alkyl-SO-C₀₋₂alkyl-, -C₀₋₂alkyl-SO₂-C₀₋₂alkyl-, -C₀₋₂alkyl-CO-C₀₋₂alkyl-, -C₀₋₂alkyl-NR⁹CO-C₀₋₂alkyl-, -C₀₋₂alkyl-NR⁹SO₂-C₀₋₂alkyl- or -heteroC₀₋₄alkyl;

W is -C₀₋₆alkylaryl optionally substituted with 1-7 independent halogen, -CN, NO₂, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR¹, -NR¹R², -C(=NR¹)NR²R³, -N(=NR¹)NR²R³, -NR¹COR², -NR¹CO₂R², -NR¹SO₂R⁴, -NR¹CONR²R³, -SR⁴, -SOR⁴, -SO₂R⁴, -SO₂NR¹R², -COR¹, -CO₂R¹, -CONR¹R², -C(=NR¹)R², or -C(=NOR¹)R² substituents;

35 Y is aryl or heteroaryl optionally substituted with 1-7 independent halogen, -CN, NO₂, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR⁵, -NR⁵R⁶, -C(=NR⁵)NR⁶R⁷, -N(=NR⁵)NR⁶R⁷, -NR⁵COR⁶, -NR⁵CO₂R⁶, -NR⁵SO₂R⁸, -NR⁵CONR⁶R⁷, -SR⁸, -SOR⁸, -SO₂R⁸, -SO₂NR⁵R⁶, -COR⁵, -CO₂R⁵, -CONR⁵R⁶, -C(=NR⁵)R⁶, or -C(=NOR⁵)R⁶

substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to Y; wherein the -C₁₋₆alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), or -N(C₀₋₆alkyl)(aryl) substituents;

R⁵, R⁶, and R⁷ each independently is -C₀₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

R⁸ is -C₁₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

B is -C₀₋₄alkyl, -C₀₋₂alkyl-SO-C₀₋₂alkyl-, -C₀₋₂alkyl-SO₂-C₀₋₂alkyl-, -C₀₋₂alkyl-CO-C₀₋₂alkyl-, -C₀₋₂alkyl-NR¹⁰CO-C₀₋₂alkyl-, -C₀₋₂alkyl-NR¹⁰SO₂-C₀₋₂alkyl- or -heteroC₀₋₄alkyl;

R⁹ and R¹⁰ each independently is -C₀₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

R¹¹, R¹² and R¹³ is each independently halogen, -C₀₋₆alkyl, -C₀₋₆alkoxyl, =O, =N(C₀₋₄alkyl), or -N(C₀₋₄alkyl)(C₀₋₄alkyl), wherein optionally two of R¹¹, R¹² and R¹³ are combined to form a cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring fused to the pyrrole moiety; wherein the -C₁₋₆alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -O(heteroaryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), or -N(C₀₋₆alkyl)(aryl) substituents;

Z is -C₃₋₇cycloalkyl, -heteroC₃₋₇cycloalkyl, -C₀₋₆alkylaryl, or -C₀₋₆alkylheteroaryl optionally substituted with 1-7 independent halogen, -CN, NO₂, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR¹, -NR¹R², -C(=NR¹)NR²R³, -N(=NR¹)NR²R³, -NR¹COR², -NR¹CO₂R², -NR¹SO₂R⁴, -NR¹CONR²R³, -SR⁴, -SOR⁴, -SO₂R⁴, -SO₂NR¹R², -COR¹, -CO₂R¹, -CONR¹R², -C(=NR¹)R², or -C(=NOR¹)R² substituents;

one of W and Z is optionally absent; and

any N may be an N-oxide.

In a sixth aspect, the compounds of this invention are represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein:

X is aryl or heteroaryl optionally substituted with 1-7 independent halogen, -CN, NO₂, -C₁-6alkyl, -C₁-6alkenyl, -C₁-6alkynyl, -OR¹, -NR¹R², -C(=NR¹)NR²R³, -N(=NR¹)NR²R³, -NR¹COR², -NR¹CO₂R², -NR¹SO₂R⁴, -NR¹CONR²R³, -SR⁴, -SOR⁴, -SO₂R⁴, -SO₂NR¹R², -COR¹, -CO₂R¹, -CONR¹R², -C(=NR¹)R², or -C(=NOR¹)R² substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to X; wherein the -C₁-6alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, -CN, -C₁-6alkyl, -O(C₀-6alkyl), -O(C₃-7cycloalkyl), -O(aryl), -N(C₀-6alkyl)(C₀-6alkyl), -N(C₀-6alkyl)(C₃-7cycloalkyl), or -N(C₀-6alkyl)(aryl) substituents;

R¹, R², and R³ each independently is -C₀-6alkyl, -C₃-7cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, -C₁-6alkyl, -O(C₀-6alkyl), -O(C₃-7cycloalkyl), -O(aryl), -N(C₀-6alkyl)(C₀-6alkyl), -N(C₀-6alkyl)(C₃-7cycloalkyl), -N(C₀-6alkyl)(aryl) substituents;

R⁴ is -C₁-6alkyl, -C₃-7cycloalkyl, heteroaryl, or aryl; optionally substituted with 1-5 independent halogen, -CN, -C₁-6alkyl, -O(C₀-6alkyl), -O(C₃-7cycloalkyl), -O(aryl), -N(C₀-6alkyl)(C₀-6alkyl), -N(C₀-6alkyl)(C₃-7cycloalkyl), -N(C₀-6alkyl)(aryl) substituents;

A is -C₀-4alkyl, -C₀-2alkyl-SO-C₀-2alkyl-, -C₀-2alkyl-SO₂-C₀-2alkyl-, -C₀-2alkyl-CO-C₀-2alkyl-, -C₀-2alkyl-NR⁹CO-C₀-2alkyl-, -C₀-2alkyl-NR⁹SO₂-C₀-2alkyl- or -heteroC₀-4alkyl;

W is -C₀-6alkylheteroaryl optionally substituted with 1-7 independent halogen, -CN, NO₂, -C₁-6alkyl, -C₁-6alkenyl, -C₁-6alkynyl, -OR¹, -NR¹R², -C(=NR¹)NR²R³, -N(=NR¹)NR²R³, -NR¹COR², -NR¹CO₂R², -NR¹SO₂R⁴, -NR¹CONR²R³, -SR⁴, -SOR⁴, -SO₂R⁴, -SO₂NR¹R², -COR¹, -CO₂R¹, -CONR¹R², -C(=NR¹)R², or -C(=NOR¹)R² substituents;

Y is aryl or heteroaryl optionally substituted with 1-7 independent halogen, -CN, NO₂, -C₁-6alkyl, -C₁-6alkenyl, -C₁-6alkynyl, -OR⁵, -NR⁵R⁶, -C(=NR⁵)NR⁶R⁷, -N(=NR⁵)NR⁶R⁷, -NR⁵COR⁶, -NR⁵CO₂R⁶, -NR⁵SO₂R⁸, -NR⁵CONR⁶R⁷, -SR⁸, -SOR⁸, -SO₂R⁸, -SO₂NR⁵R⁶, -COR⁵, -CO₂R⁵, -CONR⁵R⁶, -C(=NR⁵)R⁶, or -C(=NOR⁵)R⁶ substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to Y; wherein the -C₁-6alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, -CN, -C₁-6alkyl, -O(C₀-6alkyl), -O(C₃-7cycloalkyl), -O(aryl), -N(C₀-6alkyl)(C₀-6alkyl), -N(C₀-6alkyl)(C₃-7cycloalkyl), or -N(C₀-6alkyl)(aryl) substituents;

R⁵, R⁶, and R⁷ each independently is -C₀₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

R⁸ is -C₁₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

B is -C₀₋₄alkyl, -C₀₋₂alkyl-SO-C₀₋₂alkyl-, -C₀₋₂alkyl-SO₂-C₀₋₂alkyl-, -C₀₋₂alkyl-CO-C₀₋₂alkyl-, -C₀₋₂alkyl-NR¹⁰CO-C₀₋₂alkyl-, -C₀₋₂alkyl-NR¹⁰SO₂-C₀₋₂alkyl- or -heteroC₀₋₄alkyl;

R⁹ and R¹⁰ each independently is -C₀₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

R¹¹, R¹² and R¹³ is each independently halogen, -C₀₋₆alkyl, -C₀₋₆alkoxyl, =O, =N(C₀₋₄alkyl), or -N(C₀₋₄alkyl)(C₀₋₄alkyl), wherein optionally two of R¹¹, R¹² and R¹³ are combined to form a cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring fused to the pyrrole moiety; wherein the -C₁₋₆alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -O(heteroaryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), or -N(C₀₋₆alkyl)(aryl) substituents;

Z is -C₃₋₇cycloalkyl, -heteroC₃₋₇cycloalkyl, -C₀₋₆alkylaryl, or -C₀₋₆alkylheteroaryl optionally substituted with 1-7 independent halogen, -CN, NO₂, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR¹, -NR¹R², -C(=NR¹)NR²R³, -N(=NR¹)NR²R³, -NR¹COR², -NR¹CO₂R², -NR¹SO₂R⁴, -NR¹CONR²R³, -SR⁴, -SOR⁴, -SO₂R⁴, -SO₂NR¹R², -COR¹, -CO₂R¹, -CONR¹R², -C(=NR¹)R², or -C(=NOR¹)R² substituents;

one of W and Z is optionally absent; and

any N may be an N-oxide.

As used herein, "alkyl" as well as other groups ("groups" and substituents are used herein interchangeably) having the prefix "alk" such as, for example, alkoxy, alkanoyl, alkenyl, alkynyl and the like, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl,

sec- and tert-butyl, pentyl, hexyl, heptyl and the like. "Alkenyl", "alkynyl" and other like terms include carbon chains containing at least one unsaturated C-C bond.

The term "cycloalkyl" means carbocycles containing no heteroatoms, and includes mono-, bi- and tricyclic saturated carbocycles, as well as fused ring systems. Such fused ring systems can include one ring that is partially or fully unsaturated such as a benzene ring to form fused ring systems such as benzofused carbocycles. Cycloalkyl includes such fused ring systems as spirofused ring systems. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, decahydronaphthalene, adamantane, indanyl, indenyl, fluorenyl, 1,2,3,4-tetrahydronaphthalene and the like. Similarly, "cycloalkenyl" means carbocycles containing no heteroatoms and at least one non-aromatic C-C double bond, and include mono-, bi- and tricyclic partially saturated carbocycles, as well as benzofused cycloalkenes. Examples of cycloalkenyl include cyclohexenyl, indenyl, and the like.

The term "aryl" means an aromatic substituent which is a single ring or multiple rings fused together. When formed of multiple rings, at least one of the constituent rings is aromatic. The preferred aryl substituents are phenyl and naphthyl groups.

The term "cycloalkyloxy" unless specifically stated otherwise includes a cycloalkyl group connected by a short C₁₋₂alkyl length to the oxy connecting atom.

The term "C₀₋₆alkyl" includes alkyls containing 6, 5, 4, 3, 2, 1, or no carbon atoms. An alkyl with no carbon atoms is a hydrogen atom substituent when the alkyl is a terminal group and is a direct bond when the alkyl is a bridging group.

The term "hetero" unless specifically stated otherwise includes one or more O, S, or N atoms. For example, heterocycloalkyl and heteroaryl include ring systems that contain one or more O, S, or N atoms in the ring, including mixtures of such atoms. The hetero atoms replace ring carbon atoms. Thus, for example, a heterocycloC₅alkyl is a five-member ring containing from 4 to no carbon atoms. Examples of heteroaryls include pyridinyl, quinolinyl, isoquinolinyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinoxalinyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, pyrrolyl, indolyl, pyrazolyl, indazolyl, oxazolyl, benzoxazolyl, isoxazolyl, thiazolyl, benzothiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, and tetrazolyl. Examples of heterocycloalkyls include azetidyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, imidazolinyl, pyrrolidin-2-one, piperidin-2-one, and thiomorpholinyl.

The term "heteroC₀₋₄alkyl" means a heteroalkyl containing 3, 2, 1, or no carbon atoms. However, at least one heteroatom must be present. Thus, as an example, a heteroC₀₋₄alkyl having no carbon atoms but one N atom would be a -NH- if a bridging group and a -NH₂ if a terminal group. Analogous bridging or terminal groups are clear for an O or S heteroatom.

The term "amine" unless specifically stated otherwise includes primary, secondary and tertiary amines substituted with C₀₋₆alkyl.

The term "carbonyl" unless specifically stated otherwise includes a C₀₋₆alkyl substituent group when the carbonyl is terminal.

5 The term "halogen" includes fluorine, chlorine, bromine and iodine atoms.

The term "optionally substituted" is intended to include both substituted and unsubstituted. Thus, for example, optionally substituted aryl could represent a pentafluorophenyl or a phenyl ring. Further, optionally substituted multiple moieties such as, for example, alkylaryl are intended to mean that the aryl and the aryl groups are optionally substituted. If only one of
10 the multiple moieties is optionally substituted then it will be specifically recited such as "an alkylaryl, the aryl optionally substituted with halogen or hydroxyl."

Compounds described herein contain one or more double bonds and may thus give rise to cis/trans isomers as well as other conformational isomers. The present invention includes all such possible isomers as well as mixtures of such isomers.

15 Compounds described herein can contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. The above Formula I is shown without a definitive stereochemistry at certain positions. The present
20 invention includes all stereoisomers of Formula I and pharmaceutically acceptable salts thereof. Further, mixtures of stereoisomers as well as isolated specific stereoisomers are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

25 The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (ic and ous), ferric, ferrous,
30 lithium, magnesium, manganese (ic and ous), potassium, sodium, zinc and the like salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-
35 toxic bases from which salts can be formed include ion exchange resins such as, for example,

arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

The pharmaceutical compositions of the present invention comprise a compound represented by Formula I (or pharmaceutically acceptable salts thereof) as an active ingredient, a pharmaceutically acceptable carrier and optionally other therapeutic ingredients or adjuvants. Such additional therapeutic ingredients include, for example, i) opiate agonists or antagonists, ii) calcium channel antagonists, iii) 5HT receptor agonists or antagonists iv) sodium channel antagonists, v) NMDA receptor agonists or antagonists, vi) COX-2 selective inhibitors, vii) NK1 antagonists, viii) non-steroidal anti-inflammatory drugs ("NSAID"), ix) GABA-A receptor modulators, x) dopamine agonists or antagonists, xi) selective serotonin reuptake inhibitors ("SSRI") and/or selective serotonin and norepinephrine reuptake inhibitors ("SSNRI"), xii) tricyclic antidepressant drugs, xiv) norepinephrine modulators, xv) L-DOPA, xvi) buspirone, xvii) lithium, xviii) valproate, ix) neurontin (gabapentin), xx) olanzapine, xxi) nicotinic agonists or antagonists including nicotine, xxii) muscarinic agonists or antagonists, xxiii) heroin substituting drugs such as methadone, levo-alpha-acetylmethadol, buprenorphine and naltrexone, and xxiv) disulfiram and acamprosate. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

Creams, ointments, jellies, solutions, or suspensions containing the compound of Formula I can be employed for topical use. Mouth washes and gargles are included within the scope of topical use for the purposes of this invention.

Dosage levels from about 0.01mg/kg to about 140mg/kg of body weight per day are useful in the treatment of psychiatric and mood disorders such as, for example, schizophrenia, anxiety, depression, panic, bipolar disorders, and circadian disorders, as well as being useful in the treatment of pain which are responsive to mGluR5 inhibition, or alternatively about 0.5mg to about 7g per patient per day. For example, schizophrenia, anxiety, depression, and panic may be effectively treated by the administration of from about 0.01mg to 75mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 3.5g per patient per day. Pain may be effectively treated by the administration of from about 0.01mg to 125mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 5.5g per patient per day. Further, it is understood that the mGluR5 inhibiting compounds of this invention can be administered at prophylactically effective dosage levels to prevent the above-recited conditions.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration to humans may conveniently contain from about 0.5mg to about 5g of active agent, compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Unit dosage forms will generally contain between from about 1mg to about 1000mg of the active ingredient, typically 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, 500mg, 600mg, 800mg or 1000mg.

It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

In practice, the compounds represented by Formula I, or pharmaceutically acceptable salts thereof, of this invention can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compound represented by Formula I, or pharmaceutically acceptable salts

thereof, may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and
5 intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

Thus, the pharmaceutical compositions of this invention may include a pharmaceutically acceptable carrier and a compound or a pharmaceutically acceptable salt of Formula I. The compounds of Formula I, or pharmaceutically acceptable salts thereof, can also
10 be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil,
15 olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars,
20 microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a
30 suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.1mg to about 500mg of the active ingredient and each cachet or capsule preferably containing from about 0.1mg to about 500mg of the active ingredient. Thus, a tablet, cachet, or capsule conveniently contains 0.1mg, 1mg, 5mg, 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, or 500mg of the active ingredient taken one or two
35 tablets, cachets, or capsules, once, twice, or three times daily.

Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils.

5 Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid
10 for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

15 Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, utilizing a compound represented by Formula I of this invention, or pharmaceutically acceptable salts thereof, via conventional processing methods. As an
20 example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5 wt% to about 10 wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose
25 suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in moulds.

In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier
30 ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound described by Formula I, or pharmaceutically acceptable salts thereof, may also be prepared in powder or liquid concentrate form.

The compounds and pharmaceutical compositions of this invention have been found to exhibit biological activity as mGluR5 inhibitors. Accordingly, another aspect of the invention is the treatment in mammals of, for example, schizophrenia, anxiety, depression, panic, bipolar disorders, circadian rhythm and sleep disorders, pain, Parkinson's disease, cognitive dysfunction, epilepsy, obesity, drug addiction, drug abuse and drug withdrawal – maladies that are amenable to amelioration through inhibition of mGluR5 – by the administration of an effective amount of the compounds of this invention. The term “mammals” includes humans, as well as other animals such as, for example, dogs, cats, horses, pigs, and cattle. Accordingly, it is understood that the treatment of mammals other than humans is the treatment of clinical correlating afflictions to those above recited examples that are human afflictions.

Further, as described above, the compound of this invention can be utilized in combination with other therapeutic compounds. In particular, the combinations of the mGluR5 inhibiting compound of this invention can be advantageously used in combination with i) opiate agonists or antagonists, ii) calcium channel antagonists, iii) 5HT receptor agonists or antagonists iv) sodium channel antagonists, v) NMDA receptor agonists or antagonists, vi) COX-2 selective inhibitors, vii) NK1 antagonists, viii) non-steroidal anti-inflammatory drugs (“NSAID”), ix) GABA-A receptor modulators, x) dopamine agonists or antagonists, xi) selective serotonin reuptake inhibitors (“SSRI”) and/or selective serotonin and norepinephrine reuptake inhibitors (“SSNRI”), xii) tricyclic antidepressant drugs, xiii) norepinephrine modulators, xiv) L-DOPA, xv) buspirone, xvi) lithium, xvii) valproate, xviii) neurontin (gabapentin), xix) olanzapine, xx) nicotinic agonists or antagonists including nicotine, xxi) muscarinic agonists or antagonists, xxii) heroin substituting drugs such as methadone, levo-alpha-acetylmethadol, buprenorphine and naltrexone, and xxiii) disulfiram and acamprosate.

The abbreviations used herein have the following tabulated meanings.

Abbreviations not tabulated below have their meanings as commonly used unless specifically stated otherwise.

Ac	acetyl
AIBN	2,2'-azobis(isobutyronitrile)
BINAP	1,1'-bi-2-naphthol
Bn	benzyl
CAMP	cyclic adenosine-3',5'-monophosphate
DAST	(diethylamino)sulfur trifluoride
DEAD	diethyl azodicarboxylate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene

DIBAL	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMF	N,N-dimethylformamide
Dppf	1,1'-bis(diphenylphosphino)-ferrocene
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Et ₃ N	triethylamine
GST	glutathione transferase
HMDS	hexamethyldisilazide
LDA	lithium diisopropylamide
m-CPBA	metachloroperbenzoic acid
MMPP	monoperoxyphthalic acid
MPPM	monoperoxyphthalic acid, magnesium salt 6H ₂ O
Ms	methanesulfonyl = mesyl = SO ₂ Me
MsO	methanesulfonate = mesylate
NBS	N-bromo succinimide
NSAID	non-steroidal anti-inflammatory drug
o-Tol	ortho-tolyl
OXONE®	2KHSO ₅ •KHSO ₄ •K ₂ SO ₄
PCC	pyridinium chlorochromate
Pd ₂ (dba) ₃	Bis(dibenzylideneacetone) palladium(0)
PDC	pyridinium dichromate
PDE	Phosphodiesterase
Ph	Phenyl
Phe	Benzenediyl
PMB	para-methoxybenzyl
Pye	Pyridinediyl
r.t.	room temperature
Rac.	Racemic
SAM	aminosulfonyl or sulfonamide or SO ₂ NH ₂
SEM	2-(trimethylsilyl)ethoxymethoxy
SPA	scintillation proximity assay
TBAF	tetra-n-butylammonium fluoride
Th	2- or 3-thienyl

TFA	trifluoroacetic acid
TFAA	trifluoroacetic acid anhydride
THF	Tetrahydrofuran
Thi	Thiophenediyl
TLC	thin layer chromatography
TMS-CN	trimethylsilyl cyanide
TMSI	trimethylsilyl iodide
Tz	1H (or 2H)-tetrazol-5-yl
XANTPHOS	4,5-Bis-diphenylphosphanyl-9,9-dimethyl-9H-xanthene
C ₃ H ₅	Allyl

ALKYL GROUP ABBREVIATIONS

Me	=	Methyl
Et	=	ethyl
<i>n</i> -Pr	=	normal propyl
<i>i</i> -Pr	=	isopropyl
<i>n</i> -Bu	=	normal butyl
<i>i</i> -Bu	=	isobutyl
<i>s</i> -Bu	=	secondary butyl
<i>t</i> -Bu	=	tertiary butyl
c-Pr	=	cyclopropyl
c-Bu	=	cyclobutyl
c-Pen	=	cyclopentyl
c-Hex	=	cyclohexyl

5

ASSAYS DEMONSTRATING BIOLOGICAL ACTIVITY

The compounds of this invention were tested against the hmGluR5a receptor stably expressed in mouse fibroblast Ltk⁻ cells (the hmGluR5a/L38-20 cell line) and activity was detected by changes in [Ca⁺⁺]_i, measured using the fluorescent Ca⁺⁺-sensitive dye, fura-2. InsP

10

assays were performed in mouse fibroblast Ltk⁻ cells (LM5a cell line) stably expressing hmGluR5a. The assays described in International Patent Publication WO 0116121 can be used.

Calcium Flux Assay

5 The activity of compounds was examined against the hmGluR5a receptor stably expressed in mouse fibroblast Ltk⁻ cells (the hmGluR5a/L38 cell line). See generally Daggett et al., *Neuropharmacology* 34:871-886 (1995). Receptor activity was detected by changes in intracellular calcium ($[Ca^{2+}]_i$) measured using the fluorescent calcium-sensitive dye, fura-2. The hmGluR5a/L38-20 cells were plated onto 96-well plates, and loaded with 3 μ M fura-2 for 1h. 10 Unincorporated dye was washed from the cells, and the cell plate was transferred to a 96-channel fluorimeter (SIBIA-SAIC, La Jolla, CA) which is integrated into a fully automated plate handling and liquid delivery system. Cells were excited at 350 and 385nm with a xenon source combined with optical filters. Emitted light was collected from the sample through a dichroic mirror and a 510nm interference filter and directed into a cooled CCD camera (Princeton Instruments). Image 15 pairs were captured approximately every 1s, and ratio images were generated after background subtraction. After a basal reading of 20s, an EC₈₀ concentration of glutamate (10 μ M) was added to the well, and the response evaluated for another 60s. The glutamate-evoked increase in $[Ca^{2+}]_i$ in the presence of the screening compound was compared to the response of glutamate alone (the positive control).

Phosphatidylinositol Hydrolysis (PI) Assays

 Inositolphosphate assays were performed as described by Berridge et al. [Berridge et al, *Biochem. J.* 206: 587-5950 (1982); and Nakajima et al., *J. Biol. Chem.* 267:2437-2442 (1992)] with slight modifications. Mouse fibroblast Ltk cells expressing hmGluR5 25 (hmGluR5/L38- 20 cells) were seeded in 24-well plates at a density of 8x10⁵cells/well. One μ Ci of [³H]-inositol (Amersham PT6-271; Arlington Heights, Ill.; specific activity = 17.7 Ci/mmol) was added to each well and incubated for 16h at 37°C. Cells were washed twice and incubated for 45min in 0.5mL of standard Hepes buffered saline buffer (HBS; 125mM NaCl, 5mM KCl, 0.62mM MgSO₄, 1.8mM CaCl₂, 20mM HEPES, 6mM glucose, pH to 7.4). The cells were 30 washed with HBS containing 10mM LiCl, and 400 μ L buffer added to each well. Cells were incubated at 37°C for 20min. For testing, 50 μ L of 10X compounds used in the practice of the invention (made in HBS/LiCl (100mM)) was added and incubated for 10 minutes. Cells were activated by the addition of 10 μ M glutamate, and the plates left for 1 hour at 37°C. The incubations were terminated by the addition of 1mL ice-cold methanol to each well. In order to 35 isolate inositol phosphates (IPs), the cells were scraped from wells, and placed in numbered glass

test tubes. One mL of chloroform was added to each tube, the tubes were mixed, and the phases separated by centrifugation. IPs were separated on Dowex anion exchange columns (AG 1-X8 100-200 mesh formate form). The upper aqueous layer (750 μ L) was added to the Dowex columns, and the columns eluted with 3mL of distilled water. The eluents were discarded, and the columns were washed with 10mLs of 60mM ammonium formate/5mM Borax, which was also discarded as waste. Finally, the columns were eluted with 4mL of 800mM ammonium formate/0.1M formic acid, and the samples collected in scintillation vials. Scintillant was added to each vial, and the vials shaken, and counted in a scintillation counter after 2 hours. Phosphatidylinositol hydrolysis in cells treated with certain exemplary compounds was compared to phosphatidylinositol hydrolysis in cells treated with the agonist alone in the absence of compound.

The compounds of this application have mGluR5 inhibitory activity as shown by IC₅₀ values of less than 10 μ M in the calcium flux assay or inhibition at a concentration of 100 μ M in the PI assay. Preferably, the compounds should have IC₅₀ values of less than 1 μ M in the calcium flux assay and IC₅₀ values of less than 10 μ M in the PI assay. Even more preferably, the compounds should have IC₅₀ values of less than 500 nM in the calcium flux assay and IC₅₀ values of less than 1 μ M in the PI assay

Examples 1 to 8 have mGluR5 inhibitory activity as shown by inhibition at 10 μ M or less in the calcium flux assay or inhibition at 100 μ M or less in the PI assay.

The examples that follow are intended as an illustration of certain preferred embodiments of the invention and no limitation of the invention is implied.

Unless specifically stated otherwise, the experimental procedures were performed under the following conditions. All operations were carried out at room or ambient temperature that is, at a temperature in the range of 18-25°C. Evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000pascals: 4.5-30mm. Hg) with a bath temperature of up to 60°C. The course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only. Melting points are uncorrected and 'd' indicates decomposition. The melting points given are those obtained for the materials prepared as described. Polymorphism may result in isolation of materials with different melting points in some preparations. The structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data. When given, yields are for illustration only. When given, NMR data is in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300MHz, 400MHz or 500MHz using the indicated solvent. Conventional abbreviations used for signal

shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. broad; etc. In addition, "Ar" signifies an aromatic signal. Chemical symbols have their usual meanings; the following abbreviations are used: v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (liter(s)), mL (milliliters), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq (equivalent(s)).

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Methods of Synthesis

Compounds of the present invention can be prepared according to the following methods. The substituents are the same as in Formula I except where defined otherwise.

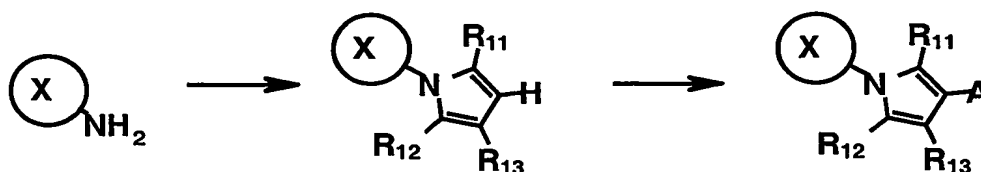
In accordance with another embodiment of the present invention, there are provided methods for the preparation of heteroaryl-substituted pyrrole compounds as described above. For example, many of the heterocyclic compounds described above can be prepared using synthetic chemistry techniques well known in the art (see *Comprehensive Heterocyclic Chemistry*, Katritzky, A. R. and Rees, C. W. eds., Pergamon Press, Oxford, 1984) from a heteroaryl-substituted pyrrole of Formula (I).

15

In Schemes 1 to 6 below, W, X, Y, Z, A and B are as defined above for Formula (I).

Other variables are understood by one in the art by the context in which they are used.

Scheme 1

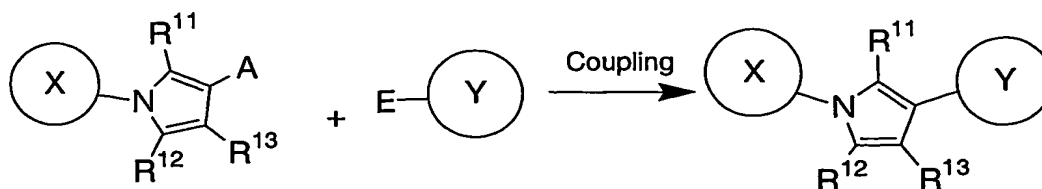


Thus in **Scheme 1**, ring system X containing an aniline moiety (prepared using synthetic chemistry techniques well known in the art) is reacted with a 1,4-dicarbonyl or its equivalent in a suitable solvent (*e.g.* EtOH, THF, DME, DMF *etc.*) at a temperature between 30°C to 150°C for 1 to 18h to form a substituted pyrrole. In turn, the 3-position of the pyrrole is derivatized with a functional group A, such as a halogen or trifluoromethanesulfonate and the like, which is capable of undergoing a metal-catalyzed cross-coupling reaction. For example, the group A may be a bromine atom which may be installed using bromotrimethylsilane (see for example Pagnoni, U.G.; Pinetti, A. *J.Heterocycl.Chem.* **1993**, 30, 617-621).

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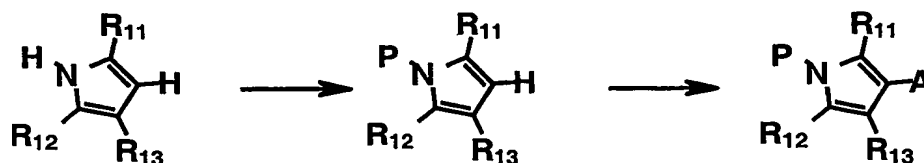
Scheme 2



In turn, the derivatized pyrrole is reacted with a moiety **Y** under metal-catalyzed cross-coupling conditions (**Scheme 2**) where **E** is a metallic or metalloid species such as $B(OR)_2$, Li , $MgHal$, SnR_3 , $ZnHal$, SiR_3 and the like which is capable of undergoing a metal-catalyzed cross-coupling reaction. The coupling may be promoted by a homogeneous catalyst such as $Pd(PPh_3)_4$, or by a heterogeneous catalyst such as Pd on carbon in a suitable solvent (*e.g.* THF, DME, toluene, MeCN, DMF, H_2O *etc.*). Typically a base, such as K_2CO_3 , NEt_3 , and the like, will also be present in the reaction mixture. Other promoters may also be used such as CsF . The coupling reaction is typically allowed to proceed by allowing the reaction temperature to warm slowly from about $0^\circ C$ up to rt over a period of several hours. The reaction mixture is then maintained at rt, or heated to a temperature anywhere between $30^\circ C$ to $150^\circ C$. The reaction mixture is then maintained at a suitable temperature for a time in the range of about 4 up to 48h, with about 18h typically being sufficient (see for example Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483). The product from the reaction can be isolated and purified employing standard techniques, such as solvent extraction, chromatography, crystallization, distillation and the like.

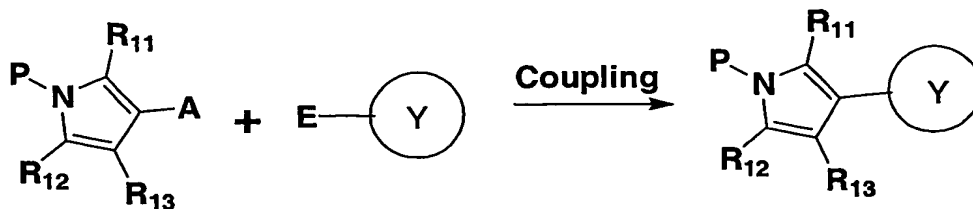
Another embodiment of the present invention is illustrated in **Scheme 3**.

Scheme 3



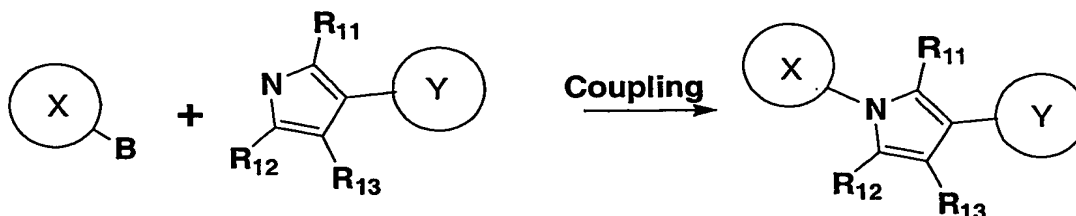
Thus, the free ring nitrogen in an optionally substituted pyrrole (prepared using synthetic chemistry techniques well known in the art) is protected with a group **P**, where **P** may be a trialkyl- or triaryl silane, arylsulfonyl or alkyl carbamate protecting group and the like. In turn, the 3-position of the pyrrole is derivatized with a functional group **A**, such as a halogen or trifluoromethanesulfonate and the like, which is capable of undergoing a metal-catalyzed cross-coupling reaction. For example, the group **A** may be an iodine which maybe installed using molecular iodine and mercuric acetate (see for example Bray, B. L. *et al. J. Org. Chem.* **1990**, *55*, 6317-6328).

Scheme 4



In turn, the derivatized pyrrole is reacted with a moiety Y under metal-catalyzed cross-coupling conditions (**Scheme 4**) where E is a metallic or metalloid species such as B(OR)₂, ZnHal, Li, MgHal, SnR₃, SiR₃ and the like which is capable of undergoing a metal-catalyzed cross-coupling reaction. The coupling may be promoted by a homogeneous catalyst such as Pd(PPh₃)₄, or by a heterogeneous catalyst such as Pd on carbon in a suitable solvent (*e.g.* THF, DME, toluene, MeCN, DMF, H₂O *etc.*). If required a base, such as K₂CO₃, NEt₃, and the like, will also be present in the reaction mixture. Other promoters may also be used such as CsF. The coupling reaction is typically allowed to proceed by allowing the reaction temperature to warm slowly from about 0°C up to rt over a period of several hours. The reaction mixture is then maintained at rt, or heated to a temperature anywhere between 30°C to 150°C. The reaction mixture is then maintained at a suitable temperature for a time in the range of about 4 up to 48h, with about 18h typically being sufficient (see for example: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483 or Negishi, E.; Liu, F. *Palladium or Nickel catalyzed Cross-coupling with Organometals Containing Zinc, Magnesium, Aluminium and Zirconium. In Metal-catalyzed Cross-coupling Reactions* Diederich, F.; Stang, P.J. Eds. Wiley, Weinheim, Germany, 1998; pp1-42). The product from the reaction can be isolated and purified employing standard techniques, such as solvent extraction, chromatography, crystallization, distillation and the like.

Scheme 5



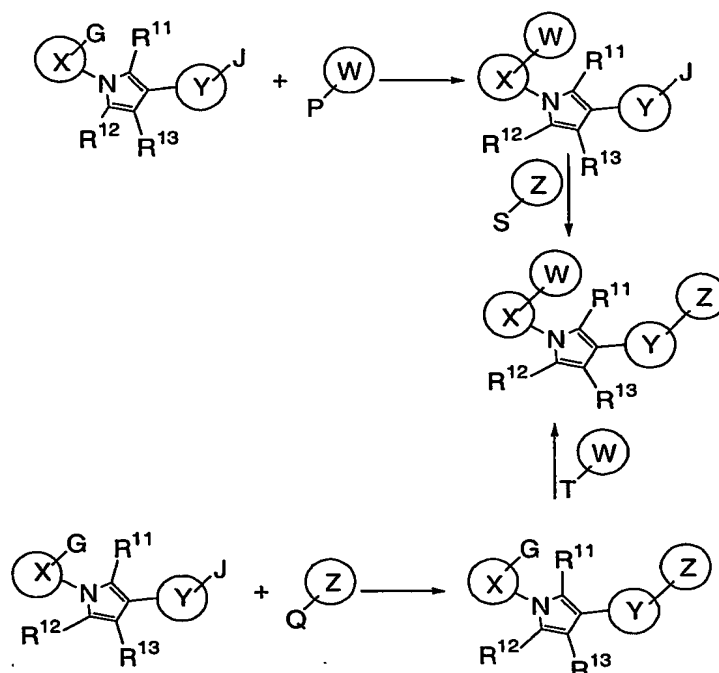
As shown in **Scheme 5**, the pyrrole may then be coupled with a species X substituted with a group B. B may be a good aryl leaving group such as F, and X is electron deficient or has one or more electron withdrawing substituents (*e.g.* NO₂, CN *etc.*), the coupling reaction may be effected thermally in a temperature range of about 60°C up to about 250°C.

Typically, this reaction is carried out in the presence of base (*e.g.* pyridine, NEt₃, Cs₂CO₃, K₂CO₃ *etc.*) in a suitable solvent, such as DMSO, DMF, DMA H₂O and the like, and takes from 1h up to about 72h with 18h typically being sufficient (see for example Russell, S. S.; Jahangir; *Synth. Commun.* 1994, 24, 123-130).

5 Alternatively, **B** may be a good leaving group capable of undergoing a metal-catalyzed cross-coupling reaction such as a halogen or trifluoromethanesulfonate and the like. Typically, the reaction is carried out using catalytic amounts of a copper (I) salt together with a diamine ligand and in the presence of a suitable base (*e.g.* K₃PO₄, Cs₂CO₃, K₂CO₃ *etc.*) in a suitable solvent, such as Dioxane, DMSO, DMA, DMF (see for example Klapers, A.; Antilla,
10 J.C.; Huang, X.; Buchwald, S.L. *J. Am. Chem. Soc.* 2001, *in press*).

In the schemes above, ring systems X and/or Y may already contain a pendant ring W and/or Z. However, if required, ring systems W and/or Z may be appended to X and/or Y respectively where G and/or J are functional groups capable of undergoing a metal catalyzed-cross coupling (such as halogen, trifluoromethane-sulfonate, B(OR)₂, ZnX, SnR₃, and the like -
15 **Scheme 6** below). Ring systems W and Z are substituted with groups P, Q, S and T which may be for example, halogen, trifluoromethanesulfonate, B(OR)₂, ZnX, SnR₃, and the like. Typically, a transition metal catalyst such as Pd(PPh₃)₄, Pd(PPh₃)₂Cl₂, Pd(OAc)₂, NiCl₂(dppe), Pd(OAc)₂, Pd₂(dba)₃, Cu(OAc)₂, CuI or the like may be employed, typically along with a suitable base such as K₂CO₃, K₃PO₄, Cs₂CO₃, Et₃N, pyridine or the like. Additionally, ligands such as
20 BINAP, di-*tert*-butyl phosphinobiphenyl, di-cyclohexylphosphino biphenyl, tri *tert*-butylphosphine, XANTPHOS, triphenylarsine and the like may be added. The reaction is carried out in a suitable solvent such as toluene, DME, dioxane, THF, water or a combination of the above and is typically heated at 50°C – 150°C for between 1 and 48 hrs. The reaction may be homogeneous or heterogeneous (see for example Miyaura, N.; Suzuki, A. *Chem. Rev.* 1995, 95, 2457-2483 and Dai, C.; Fu, G.C. *J. Am. Chem. Soc.*, 2001, 123, 2719-2724 and Littke, A.F.; Fu, G.C. *Angew. Chem. Int. Ed.* 1999, 38, 6, 2411-2413 and Dai, C.; Fu, G.C. *J. Am. Chem. Soc.* 2001, 123, 2719-2724).

Scheme 6



Alternatively ring systems W or Z may be a nitrogen containing heterocycle wherein the nitrogen is directly attached to the ring system X or Y respectively. In this case G and/or J are groups capable of undergoing a metal catalyzed N-aryl cross-coupling (such as halogen,

- 5 trifluoromethane-sulfonate, B(OR)₂, ZnX, SnR₃, and the like – **Scheme 6**). Typically a transition metal such as CuI, Cu(OAc)₂, Cu(OTf)₂, Pd(PPh₃)₄, Pd(PPh₃)₂Cl₂, Pd(OAc)₂, Pd₂(dba)₃, NiCl₂(dppe) is used along with a suitable base such as K₂CO₃, K₃PO₄, Cs₂CO₃, NaOtBu or the like. Additionally, phosphine containing ligands such as BINAP, di-*tert*-butyl phosphinobiphenyl, di-cyclohexylphosphino biphenyl, tri *tert*-butylphosphine, XANTPHOS and the like may be added. Further, additives such as 1,10-phenanthroline, 1,2-diaminocyclohexane, dibenzylideneacetone may be used. The reaction is typically carried out in a solvent such as toluene, DME, dioxane, THF, water or a combination of the above and is typically heated at 50°C – 150°C for between 1 and 48 hrs. The reaction may be homogeneous or heterogeneous. The product from **Scheme 4**, can be isolated and purified employing standard techniques, such as
- 15 solvent extraction, acid-base extraction, chromatography, crystallization, distillation and the like (see for example Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Cham, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, 39, 2941-2944 and Kiyomori, A.; Marcoux, J. F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, 40, 2657-2660 and Wolfe, J.P.; Tomori, H.; Sadighi, J.P.; Yin, J.; Buchwald, S.L. *J. Org. Chem.*, **2000**, 65, 1158-1174 and Yin, J.; Buchwald, S.L.;
- 20 *Org. Lett.*, **2000**, 2, 1101-1104).

In addition, many of the heterocyclic intermediate compounds described above can be prepared using other synthetic chemistry techniques well known in the art (see *Comprehensive Heterocyclic Chemistry*, Katritzky, A. R. and Rees, C. W. eds., Pergamon Press, Oxford, 1984) and references cited there within.

5

COMPOUND 1

2-(1H-Pyrrol-3-yl)pyridine

2-(1H-Pyrrol-3-yl)pyridine was prepared according to the method of Nicholas D.

10 Smith, Dehua Huang, and Nicholas D. P. Cosford. *Org. Lett.* **2002**, Vol. 4, No. 20, 3537-3539.

COMPOUND 2

3-(3-Iodophenyl)pyridine

A solution of 1,3-diiodobenzene (1.10 g, 3.3 mmol), 3-(diethylboryl)pyridine (0.48 g, 3.3 mmol), tetrakis(triphenylphosphine)palladium(0) (0.010 g, 0.0086 mmol) potassium carbonate (0.922 g, 6.64 mmol), in mixed solvent of 3 mL DMF and 1mL water, was heated at 150°C for 5 minutes under microwave irradiation. The reaction mixture was quenched with H₂O (30 mL), then extracted with EtOAc (3 x 30 mL) and the combined organic extracts washed with brine. The organic phase was dried over Na₂SO₄ and concentrated *in vacuo*. The crude purified by liquid chromatography on silica gel using an ISCO single channel system (Hexane/EtOAc= 9/1 to 1/9) to afford 3-(3-iodophenyl)pyridine as a yellow oil.

¹H NMR (CDCl₃ 500 MHz) δ 8.80 (s, br, 1H), 8.62 (s, br, 1H), 7.92 (s, 1H), 7.83-7.82 (d, 1H), 7.74-7.72 (m, 1H), 7.54-7.52 (m, 1H), 7.38-7.36 (dd, 1H), 7.22-7.19 (m, 1H).

EXAMPLE 1

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2-[1-(3-Pyridin-3-ylphenyl)-1H-pyrrol-3-yl]pyridine

A solution of 2-(1H-pyrrol-3-yl)pyridine (0.144 g, 1.0 mmol), 3-(3-iodophenyl)pyridine (0.281 g, 1.2 mmol), 1,10-phenanthroline (0.360 g, 2 mmol), Potassium phosphate (0.445 g, 2.1 mmol), in dioxane (3 mL) was degassed with argon for 5 minutes, followed by the addition of copper (I) iodide (0.038 g, 0.2 mmol). The reaction mixture was heated at 110°C for 4 hr. The reaction mixture was quenched with H₂O (30 mL), then extracted with EtOAc (3 x 30 mL) and

the combined organic extracts washed with brine. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The crude purified by liquid chromatography on silica gel using an ISCO single channel system (Hexane/EtOAc= 9/1 to 1/9) to afford 2-[1-(3-pyridin-3-ylphenyl)-1H-pyrrol-3-yl]pyridine as a slightly yellow oil. The free base in anhydrous diethyl ether was treated with 1.5 equivalents HCl (1M in ether) to give the HCl salt.

^1H NMR (d_4 -methanol 500 MHz) δ 9.33 (s, 1H), 8.98-8.96 (d, 1H), 8.88-8.87 (d, 1H), 8.61-8.58 (m, 2H), 8.50-8.47 (m, 1H), 8.40-8.39 (d, 1H), 8.16-8.14 (m, 2H), 7.87-7.83 (m, 2H), 7.79-7.74 (m, 2H), 7.69-7.68 (m, 1H), 7.139-7.135 (m, 1H). MS (ESI) 298.1 ($\text{M}^+\text{+H}$).

COMPOUND 3

2-(2-Methoxy-4-nitrophenyl)pyridine

A solution of 1-bromo-2-methoxy-4-nitrobenzene (7 g, 30.17 mmol), bromo(pyridin-2-yl)zinc (80 mL of 0.5M in THF, 40 mmol), tetrakis(triphenylphosphine)palladium(0) (1.7 g, 1.47 mmol) in 70 mL THF was degassed with nitrogen for 10 minutes, then heated at 63°C for 6 hr.

The reaction mixture was quenched with H_2O (30 mL), then extracted with EtOAc (3 x 30 mL) and the combined organic extracts washed with brine. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The crude purified by liquid chromatography on silica (EtOAc/Hexane 3/7) to give 2-(2-methoxy-4-nitrophenyl)pyridine. MS (ESI) 231 ($\text{M}^+\text{+H}$).

COMPOUND 4

3-Methoxy-4-pyridin-2-ylaniline

To a solution of 2-(2-methoxy-4-nitrophenyl)pyridine (5.4 g, 23.3 mmol), dimethyl hydrazine (14 mL, 233 mmol), charcoal (0.7 g), in methanol (200 mL) was added iron trichloride (0.075 g, 0.46 mmol), then heated at 65°C overnight. The reaction mixture was quenched with H_2O (50 mL), then extracted with EtOAc (3 x 50 mL) and the combined organic extracts washed with brine. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The crude

purified by liquid chromatography on silica (EtOAc/Hexane 3/7) to give 3-methoxy-4-pyridin-2-ylaniline.

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COMPOUND 5

3-(3-Iodophenyl)pyridine

Concentrated hydrochloric acid (20 mL, 240 mmol) was added to 3-methoxy-4-pyridin-2-ylaniline (4.0 g, 20 mmol) in 10 mL water at 0°C, stirred until homogeneous, then NaNO₂ (2.5 g, 36 mmol) in 10 mL water was added dropwise, after 15 minutes at 0°C, potassium iodide (6.6 g, 40 mmol) in 10 mL water was added dropwise. After 30 minutes, the reaction mixture was heated to 100°C and stirred for 30 minutes. The reaction was then cooled to room temperature and quenched with H₂O (30 mL), then extracted with EtOAc (3 x 30 mL) and the combined organic extracts washed with brine. The organic phase was dried over Na₂SO₄ and concentrated *in vacuo*. The crude was purified by liquid chromatography on silica (EtOAc/Hexane 3/7) afford 3-(3-iodophenyl)pyridine.

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EXAMPLE 2

2-[1-(3-Methoxy-4-pyridinium-2-ylphenyl)-1H-pyrrol-3-yl]pyridinium dichloride

2-(1H-Pyrrol-3-yl)pyridine (143 mg, 1 mmol), 3-(3-iodophenyl)pyridine (310 mg, 1 mmol), CuI (20 mg, 0.05 mmol), 1,2-diaminocyclohexane (36 µL, 0.15 mmol) and K₂CO₃ (290 mg, 2.1 mmol) in 1,4-dioxane (2 mL) were heated under N₂ at 105 C for 18 hours; Then in the

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SmithCreator Microwave at 165 C for 7 min. The reaction mixture was then shaken with EtOAc and NH₃ (10%)/NH₄Cl(sat) (1/1). The organic layer was separated and the aqueous layer washed with EtOAc (3X). Drying over Na₂SO₄ and concentration gave a solid that was purified by LC (hexane/EtOAc = 1/1 to 0/1) to give a yellow oil (202 mg) that was then dissolved in ether and
5 treated with 1N HCl in ether to give the HCl salt. H-NMR (d4-MeOH, 500 MHz) 8.98 (s, 1H), 8.85 (m, 1H), 8.68 (m, 1H), 8.48 (m, 1H), 8.38 (m, 1H), 8.35-8.40 (m, 2H), 8.17 (m, 1H), 7.92 (dd, 1H), 7.89 (m, 1H), 7.72-7.77 (m, 2H), 7.57 (s, 1H), 7.52 (d, 1H), 7.32 (s, 1H), 2.51 (s, 3H)

COMPOUND 6

10

1-(Triisopropylsilyl)-1H-pyrrol-3-ylboronic acid

To -78°C solution of 3-bromo-1-(triisopropylsilyl)-1H-pyrrole (0.619 g, 2.288 mmol) in 10 mL THF was added *tert*-butyllithium (2.83 mL of 1.7 M in Heptane, 4.80 mmol) dropwise. The reaction mixture was stirring at -78°C for 45 minutes, then trimethylborate (2.38 g, 22.88 mmol) was added. The reaction was stirred for another 45 minutes at -78°C. To this was then
15 added 0.9 mL methanol and water solution (V/V=1:1) and the reaction was allowed warm to room temperature. The reaction mixture was quenched with H₂O (30 mL), then extracted with EtOAc (3 x 30 mL) and the combined organic extracts washed with brine. The organic phase was dried over Na₂SO₄ and concentrated *in vacuo*, and used in the next step without further purification.

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COMPOUND 7

2-[1-(Triisopropylsilyl)-1H-pyrrol-3-yl]-1,3-thiazole

A solution of 1-(triisopropylsilyl)-1H-pyrrol-3-ylboronic acid (0.274 g, 0.46 mmol, based on presumed 45% yield of previous step), 2-bromo-1,3-thiazole (0.206 g, 1.2 mmol), potassium carbonate (0.1736, 1.2 mmol), tetrakis(triphenylphosphine)palladium(0) (0.040 g, 0.035 mmol)

in mixed solvent of benzene/water/methanol (10 mL/1 mL/1 mL), was degassed for 5 minutes, then refluxed at 90°C for overnight. The reaction mixture was quenched with H₂O (30 mL), then extracted with EtOAc (3 x 30 mL) and the combined organic extracts washed with brine. The organic phase was dried over Na₂SO₄ and concentrated *in vacuo*. The crude purified by

5 liquid chromatography on silica gel using an ISCO single channel system (Hexane/EtOAc= 9/1 to 1/9) to afford 2-[1-(triisopropylsilyl)-1*H*-pyrrol-3-yl]-1,3-thiazole as a yellow oil.

¹H NMR (CD₃Cl 500 MHz) δ 7.68 (d, 1H), 7.37-7.36 (m, 1H), 7.08 (d, 1H), 6.76-6.75 (m, 1H), 6.709-6.695 (m, 1H), 1.49-1.42 (m, 3H), 1.16-1.08 (d, 18H). MS (ESI) 307.1 (M⁺+H).

COMPOUND 8

2-(1*H*-Pyrrol-3-yl)-1,3-thiazole

To a stirred solution of 2-[1-(triisopropylsilyl)-1*H*-pyrrol-3-yl]-1,3-thiazole (200 mg, 0.65 mmol) in 2 mL THF was added dropwise tetrabutylammonium fluoride (0.98 mL of 1M in THF, 0.98 mmol), after 20 minute the reaction was quenched with H₂O (30 mL), then extracted with EtOAc (3 x 30 mL) and the combined organic extracts washed with brine. The organic phase
15 was dried over Na₂SO₄ and concentrated *in vacuo*. The crude purified by liquid chromatography on silica gel using an ISCO single channel system (Hexane/EtOAc= 9/1 to 1/9) to afford 2-(1*H*-pyrrol-3-yl)-1,3-thiazole as a yellow oil.

¹H NMR (CD₃Cl 500 MHz) δ 9.20 (br, 1H), 7.63 (d, 1H), 7.28 (d, 1H), 7.06 (d, 1H), 6.74-6.72 (m, 1H), 6.57-6.56 (m, 1H).

EXAMPLE 3

3-{3-[3-(1,3-Thiazol-2-yl)-1*H*-pyrrol-1-yl]phenyl}pyridine

A solution of 2-(1*H*-pyrrol-3-yl)-1,3-thiazole (0.100 g, 0.67 mmol) 3-(3-iodophenyl)pyridine (0.224 g, 0.8 mmol), copper (I) iodide (0.038 g, 0.2 mmol), 1,10-

phenanthroline (0.360 g, 2 mmol), potassium phosphate (0.440 g, 2.0 mmol) in dioxane (2 mL) was heated at 220°C for 1/2hr under microwave irradiation. The reaction mixture was quenched with H₂O (30 mL), then extracted with EtOAc (3 x 30 mL) and the combined organic extracts washed with brine. The organic phase was dried over Na₂SO₄ and concentrated *in vacuo*. The crude purified by liquid chromatography on silica gel using an ISCO single channel system (EtOAc 100%) to afford 3-{3-[3-(1,3-thiazol-2-yl)-1*H*-pyrrol-1-yl]phenyl}pyridine as a slightly yellow oil. The free base in anhydrous diethyl ether was treated with 1.5 equivalent HCl (1M in Ether) to give HCl salt.

¹H NMR (d₄-Methanol 500 MHz) δ 9.38 (s, 1H), 9.10-9.08 (m, 1H), 8.928-8.917 (d, 1H), 8.516-8.508 (m, 1H), 8.26-8.24 (dd, 1H), 8.178-8.175 (d, 1H), 8.123-8.115 (d, 1H), 7.92-7.86 (m, 3H), 7.82-7.78 (m, 1H), 7.70-7.69 (m, 1H), 7.04-7.03 (dd, 1H). MS (ESI) 303.97 (M⁺+H).

EXAMPLE 4

2-{2-Methoxy-4-[3-(1,3-thiazol-2-yl)-1*H*-pyrrol-1-yl]phenyl}pyridine

A solution of 2-(1*H*-pyrrol-3-yl)-1,3-thiazole (0.100 g, 0.67 mmol) 3-(3-iodophenyl)pyridine (0.248 g, 0.8 mmol), copper (I) iodide (0.038 g, 0.2 mmol), 1,10-Phenanthroline (0.360 g, 2 mmol), potassium phosphate (0.440 g, 2.0 mmol) in dioxane (2 mL) was heated to 200°C for 1/2hr under microwave irradiation. The reaction mixture was quenched with H₂O (30 mL), then extracted with EtOAc (3 x 30 mL) and the combined organic extracts washed with brine. The organic phase was dried over Na₂SO₄ and concentrated *in vacuo*. The crude purified by liquid chromatography on silica gel using an ISCO single channel system (EtOAc 100%) to give 2-{2-methoxy-4-[3-(1,3-thiazol-2-yl)-1*H*-pyrrol-1-yl]phenyl}pyridine as a slightly yellow oil. The free base in anhydrous diethyl ether was treated with 1.5 equivalent HCL (1M in Ether) to give HCl salt.

¹H NMR (d₄-Methanol 500 MHz) δ 8.878-8.866 (d, 1H), 8.72-8.69 (m, 1H), 8.60 (s, 1H), 8.37-8.35 (d, 1H), 8.143-8.135 (d, 1H), 8.08-8.05 (m, 1H), 7.94-7.93 (d, 1H), 7.92-7.90 (d, 1H), 7.76-7.75 (m, 1H), 7.595-7.591 (d, 1H), 7.56-7.54 (dd, 1H), 7.07-7.06 (dd, 1H), 4.11 (s, 3H). MS (ESI) 334.07 (M⁺+H).

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COMPOUND 9

2-(4-Bromo-2-fluorophenyl)pyridine

1-Bromo-3-fluoro-4-iodo benzene (5.0 g, 16.6 mmol), 2-pyridylzinc bromide (7.4 g, 33.2 mmol) were combined in dry THF (100 mL) under argon and Pd(PPh₃)₄ (1.9 g, 1.6 mmol) was added.

10 The reaction mixture was heated at 70°C overnight. The reaction mixture was allowed to cool to ambient temperature. TLC analysis showed no starting material present. The reaction mixture was diluted with EtOAc (300 mL), and washed with H₂O (3X100 mL), brine (300 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo to afford a dark oil. The crude product was purified by column chromatography eluting with 1:9 EtOAc: Hexane to afford 2-(4-bromo-2-

15 fluorophenyl)pyridine (2.0 g, 50 % yield) as a yellow solid. MS 254.1 (M⁺+H).

COMPOUND 10

5-Bromo-2-pyridin-2-ylbenzonitrile

2-(4-Bromo-2-fluorophenyl)pyridine (1.0 g, 3.9 mmol) and sodium cyanide (214 mg, 4.3 mmol) were combined in DMSO (20 mL) under argon. The reaction mixture was heated at 180°C

20 overnight. TLC analysis showed no starting material present. The reaction mixture was diluted with EtOAc (100 mL), and washed with H₂O (3X100 mL), brine (100 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo to afford a dark oil. The crude product was purified by

column chromatography eluting with 1:9 EtOAc: Hexane. to afford 5-bromo-2-pyridin-2-ylbenzonitrile (800 mg, 80%). MS 262.1 ($M^+ + H$).

EXAMPLE 5

2-Pyridin-2-yl-5-(3-pyridin-2-yl-1H-pyrrol-1-yl)benzonitrile

5 2-(1H-Pyrrol-3-yl)pyridine (300 mg, 2.0 mmol) , 5-bromo-2-pyridin-2-ylbenzonitrile (538.7 g, 2.0 mmol) , sodium tert-butoxide (384 mg, 4.0 mmol) and *trans*-1,2 diaminocyclohexane (23 mg, 0.2 mmol) were combined in DMF (10 mL) under argon. The reaction mixture was heated at 140°C overnight. The reaction mixture was allowed to cool to ambient temperature. TLC analysis showed no starting material present. The reaction mixture was diluted with EtOAc (100
10 mL), and washed with H₂O (3X100 mL), brine (100 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo to afford a dark oil. The crude product was purified by column chromatography eluting with 5.5:4.5 EtOAc:Hexane to afford 2-pyridin-2-yl-5-(3-pyridin-2-yl-1H-pyrrol-1-yl)benzonitrile (160 mg, 27 % yield) as a yellow solid. ¹H NMR (CDCl₃, 300 MHz) δ 8.73-8.74(d, 1H), 8.48 –8.49 (d, 1H), 8.14-8.15 (d, 1H), 7.98-8.01(m, 3H), 7.92-7.94 (d, 1H),
15 7.86-7.88(d, 1H), 7.79-7.81(t, 1H), 7.47-7.53(m, 2H), 7.22-7.24 (m, 1H), 6.94-6.95 (m, 1H). MS 323.4 ($M^+ + H$).

COMPOUND 11

2-[1-(3-Bromo-5-fluorophenyl)-1H-pyrrol-3-yl]pyridine

20 2-(1H-Pyrrol-3-yl)pyridine (2.0 g, 17 mmol) , 1-bromo-3,5-difluorobenzene(6.6 g, 34 mmol) , potassium carbonate (2.4 g, 34 mmol) were combined in DMF (30 mL) under argon. The reaction mixture was heated at 140°C overnight. The reaction mixture was allowed to cool to ambient temperature. TLC analysis showed no starting material present. The reaction mixture

was diluted with EtOAc (300 mL), and washed with H₂O (3X300 mL), brine (100 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo to afford a dark oil which solidified when pumped down under high vacuum. The crude product was purified by column chromatography eluting with 2:8 EtOAc: hexanes to afford 2-[1-(3-bromo-5-fluorophenyl)-1*H*-pyrrol-3-yl]pyridine (1.5 g, 35 % yield) as a yellow solid. ¹H NMR (CDCl₃, 300 MHz) δ 8.61-8.62(d, 1H), 8.50-8.53 (t, 1H), 8.40 (s, 1H), 8.35-8.36 (d, 1H), 7.78-7.81(m, 2H), 7.57-7.62(m, 1H), 7.54-7.57 (d, 1H), 7.43-7.46 (d, 1H), 7.11 (s, 1H), MS 319.1 (M⁺+H).

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EXAMPLE 6

3'-Fluoro-5'-(3-pyridin-2-yl-1*H*-pyrrol-1-yl)-1,1'-biphenyl-2-carbonitrile

2-[1-(3-Bromo-5-fluorophenyl)-1*H*-pyrrol-3-yl]pyridine (647 mg, 2.0 mmol) , 2-cyanophenyl boronic acid (300 mg, 2.0 mmol) , potassium carbonate (500 mg, 3.0 mmol) were combined in DME:H₂O (10:3 mL) under argon and Pd(PPh₃)₄ (231 mg, 0.2 mmol) was added and the argon flow was continued for 10 min. The reaction mixture was heated at 80°C overnight. The reaction mixture was allowed to cool to ambient temperature. TLC analysis showed no starting material present. The reaction mixture was diluted with EtOAc (100 mL), and washed with H₂O (3X100 mL), brine (100 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo to afford a dark oil. The crude product was purified by column chromatography eluting with 3.5:6.5 EtOAc: Hexane to afford 3'-fluoro-5'-(3-pyridin-2-yl-1*H*-pyrrol-1-yl)-1,1'-biphenyl-2-carbonitrile (480 mg, 70 % yield) as a yellow solid. ¹H NMR (CDCl₃, 300 MHz) δ 8.94(s, 1H), 8.70-8.72 (d, 1H), 8.46-8.49

(t, 1H), 8.33-8.35 (d, 1H), 8.03-8.05 (d, 1H), 7.83-7.95(m, 4H), 7.79-7.81 (d, 1H), 7.64-7.74 (m, 2H), 7.51-7.53 (d, 1H), 7.40 (s, 1H). MS 340.0 ($M^+ + H$).

EXAMPLE 7

5 4-[3-Fluoro-5-(3-pyridin-2-yl-1H-pyrrol-1-yl)phenyl]-3-methylpyridine

2-[1-(3-Bromo-5-fluorophenyl)-1H-pyrrol-3-yl]pyridine (463 mg, 1.46 mmol) , 4-methylpyridin-3-ylboronic acid (200 mg, 1.46 mmol) , potassium carbonate (500 mg, 3.0 mmol) were combined in toluene: methanol (10:2 mL) under argon and Pd(PPh₃)₄ (231 mg, 0.2 mmol) was added and the argon flow was continued for 10 min. The reaction mixture was heated at 90°C overnight.

10 The reaction mixture was allowed to cool to ambient temperature. TLC analysis showed no starting material present. The reaction mixture was diluted with EtOAc (100 mL), and washed with H₂O (3X100 mL), brine (100 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo to afford a dark oil. The crude product was purified by column chromatography eluting with 3.5:6.5 EtOAc: Hexane to afford

15 4-[3-fluoro-5-(3-pyridin-2-yl-1H-pyrrol-1-yl)phenyl]-3-methylpyridine (280 mg, 59 % yield) as a yellow solid. ¹H NMR (CDCl₃, 300 MHz) δ 8.91(s, 1H), 8.81-8.82 (d, 1H), 8.62-8.63 (d, 2H), 8.51-8.54 (t, 1H), 8.40-8.42 (d, 1H), 8.13-8.15(d, 1H), 7.75-7.81 (m, 3H); 7.70 (s, 1H), 7.40-7.42 (d, 1H), 7.17 (s, 1H), 2.75 (s, 3H). MS 330.1 ($M^+ + H$).

COMPOUND 12

20 2-Chloro-6-(3-pyridin-2-yl-1H-pyrrol-1-yl)pyridine

To a solution of 2-(1H-pyrrol-3-yl)pyridine (432 mg, 3.0 mmol) in DMF (15 mL) at 50°C was added NaH (3.15 mmol, 60% suspension in oil). After 10 min, 2,6-dichloropyridine (1.33 g, 9.0 mmol) was added, and the reaction was warmed to 120°C, stirred for 18h, then quenched with

water (100 mL) and partitioned with EtOAc (100 mL). The aqueous layer was washed with additional EtOAc (2x75 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified by liquid chromatography on SiO₂ eluting with 1:1 hexanes:EtOAc to afford 2-chloro-6-(3-pyridin-2-yl-1*H*-pyrrol-1-yl)pyridine as a tan solid. H-NMR (CDCl₃, 500 MHz) δ 8.60 (d, 1H), 8.13 (dd, 1H), 7.66-7.79 (m, 2H), 7.57-7.61 (m, 2H), 7.31 (d, 1H), 7.16 (d, 1H), 7.11 (dd, 1H), 6.88 (m, 1H).

EXAMPLE 8

6-(3-Pyridin-2-yl-1*H*-pyrrol-1-yl)-2,3'-bipyridine

2-Chloro-6-(3-pyridin-2-yl-1*H*-pyrrol-1-yl)pyridine (256 mg, 1.0 mmol), diethyl-(3-pyridyl)borane (162 mg, 1.1 mmol), bis(triphenylphosphine)palladium dichloride (35 mg, 0.05 mmol), and potassium carbonate (345 mg, 2.5 mmol) were combined in 3 mL of 1:1 DME:H₂O and heated via microwave irradiation for 5 min at 160°C. The reaction was diluted with 50 mL EtOAc and partitioned with H₂O (50 mL). The EtOAc layer was dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude material was purified by SiO₂ chromatography, eluting with a 20-75% EtOAc in hexanes gradient to afford 6-(3-pyridin-2-yl-1*H*-pyrrol-1-yl)-2,3'-bipyridine as a tan solid that was dissolved in ether and precipitated as an HCl salt by slow addition of 6 equivalents of 1N HCl in ether. H-NMR (CD₃OD, 500 MHz) δ 9.82 (s, 1H), 9.48 (d, 1H), 9.14 (dd, 1H), 8.95 (d, 1H), 8.62 (d, 1H), 8.52 (dd, 1H), 8.44 (d, 1H), 8.28 (dd, 1H), 8.17-8.25 (m, 2H), 8.04 (m, 1H), 7.95 (d, 1H), 7.78 (dd, 1H), 7.15 (m, 1H). MS (ESI) 299.44 (M+H⁺).

Other variations or modifications, which will be obvious to those skilled in the art, are within the scope and teachings of this invention. This invention is not to be limited except as set forth in the following claims.